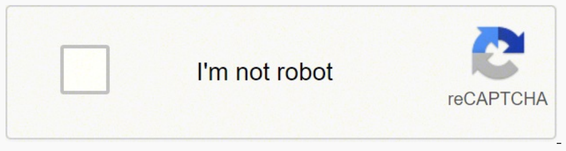

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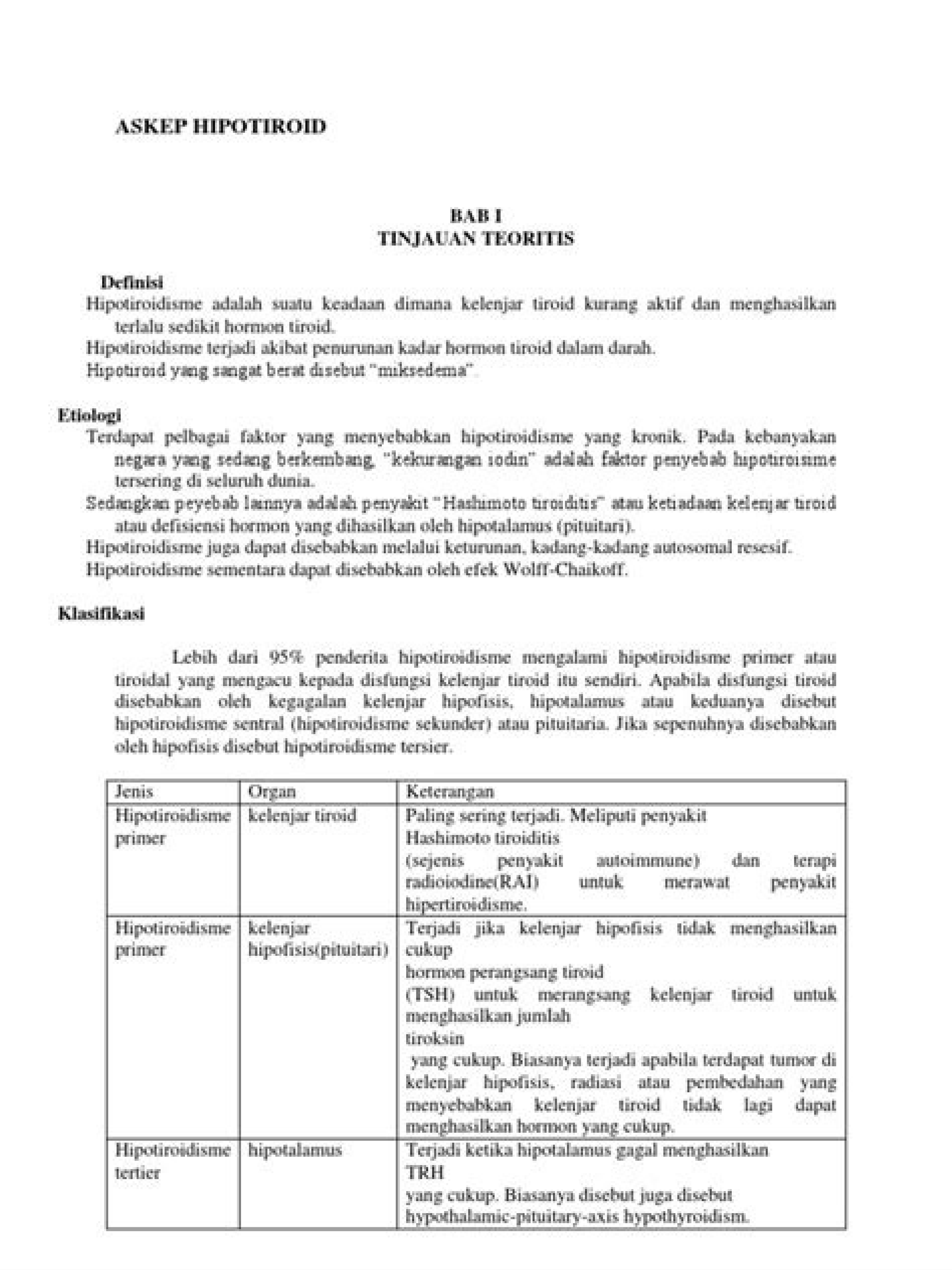

ASKEP HIPOTIROID

BAB I
TINJAUAN TEORITIS

Definisi

Hipotiroidisme adalah suatu keadaan dimana kelenjar tiroid kurang aktif dan menghasilkan terlalu sedikit hormon tiroid.

Hipotiroidisme terjadi akibat penurunan kadar hormon tiroid dalam darah.

Hipotiroid yang sangat berat disebut "miksedema".

Etiologi

Terdapat pelbagai faktor yang menyebabkan hipotiroidisme yang kronik. Pada kebanyakan negara yang sedang berkembang, "kekurangan iodin" adalah faktor penyebab hipotiroisme tersering di seluruh dunia.

Sedangkan peyebab lainnya adalah penyakit "Hashimoto tiroiditis" atau ketiadaan kelenjar tiroid atau defisiensi hormon yang dihasilkan oleh hipotalamus (pituitari).

Hipotiroidisme juga dapat disebabkan melalui keturunan, kadang-kadang autosomal resesif.

Hipotiroidisme sementara dapat disebabkan oleh efek Wolff-Chaikoff.

Klasifikasi

Lebih dari 95% penderita hipotiroidisme mengalami hipotiroidisme primer atau tiroidal yang mengacu kepada disfungsi kelenjar tiroid itu sendiri. Apabila disfungsi tiroid disebabkan oleh kegagalan kelenjar hipofisis, hipotalamus atau keduanya disebut hipotiroidisme sentral (hipotiroidisme sekunder) atau pituitaria. Jika sepenuhnya disebabkan oleh hipofisis disebut hipotiroidisme tersier.

Jenis	Organ	Keterangan
Hipotiroidisme primer	kelenjar tiroid	Paling sering terjadi. Meliputi penyakit Hashimoto tiroiditis (sejenis penyakit autoimmune) dan terapi radioiodine(RAI) untuk merawat penyakit hipertiroidisme.
Hipotiroidisme primer	kelenjar hipofisis(pituitari)	Terjadi jika kelenjar hipofisis tidak menghasilkan cukup hormon perangsang tiroid (TSH) untuk merangsang kelenjar tiroid untuk menghasilkan jumlah tiroksin yang cukup. Biasanya terjadi apabila terdapat tumor di kelenjar hipofisis, radiasi atau pembedahan yang menyebabkan kelenjar tiroid tidak lagi dapat menghasilkan hormon yang cukup.
Hipotiroidisme tertier	hipotalamus	Terjadi ketika hipotalamus gagal menghasilkan TRH yang cukup. Biasanya disebut juga disebut hypothalamic-pituitary-axis hypothyroidism.

Edema palpebral causas. Edema palpebral unilateral. Edema palpebral.

D.M. Guseva: None. coli isolates also carried a CTX-M gene (which variant was not determined). Therefore, the genetic burden of GBA1 variants and the exact genotype-phenotype correlation is still a hot topic today. Result: We integrated 1,139 genes, 1,022 copy number variations and structural variations, 2,641 single-nucleotide variations or small insertions/deletions and 36 linkage regions associated with CHD from 1,150 publications. Soto: None. Materials and Methods: MEDLINE, EMBASE, PsycINFO and CINAHL databases were searched through to July 2020 for studies that reported primary qualitative data of primary care clinicians and patient views. Heilbronner: None. M.S. Nazarenko M.S.: None. Pienkos: None. IP is caused by mutations in the IKBKG (NEMO) gene and inherited in an X-linked dominant manner with high penetrance. Hoverter: A. A diagnostic pipeline was developed using previous research results and laboratory testing procedures were validated. We generated a list of human genes encoding proteins with cytokine/chemokine and cytokine/chemokine receptor activity employing the QuickGO database (n = 314). Results: The affected individuals present with a severe neurodevelopmental disorder including congenital microcephaly, brain atrophy, corpus callosum hypoplasia, growth retardation, hypotonia and a severe developmental delay. I.A. Koroleva: None. Albiñana: None. Results: One patient, a 2-year-old male, presented with developmental delay, facial dysmorphisms, hypotonia, coloboma, cryptorchidism, plagiobrachycephaly and single umbilical artery. Variants in CACNA1A are classically related to episodic ataxia type 2, familial hemiplegic migraine type 1 or spinocerebellar ataxia type 6. Results: No associations between clinicopathological variables and SNPs were observed. Materials and methods: A partial homozygous deletion of the TM and CT domains of the BST2 gene was obtained using CRISPR/Cas9. Introduction: Pre-implantation genetic testing (PGT) can be used to prevent passing on genetic conditions to future offspring or to improve reproductive success. Mutation-negative patients underwent NGS analysis using an extended ciliary targeted panel. Previous studies showed that more than half of cases are sporadic but the exact proportion of de novo cases is still unknown. A further analysis found a novel mutation in PIEZO2 gene (Cr. 18p11, c.3539_3572delAGTATTTCATCTGCATTGGCATCCCACCTGCTCC, p.(Gln1180Leufs*19)),combined with a second mutation (c.18885G>T, p.(Glu*)) found in less than 0.001% of population. Variants were classified according to ACMG_guidelines. Hudler: None. In conclusion, our results demonstrated the efficiency of WES analysis on the identification of PVs in ID/ASD patients. J.M. Dupont: None. CD58 rs1414273 did not sustain risk association (p = 0.37). P06.035.D Modern approaches to the diagnosis of Methylmalonic academia/aciduria Vita Antsupova 1, Iryna Lastivka2, Larysa Sheiko3, Ljudmila Brisevac3, Iana Ushko1, Volodymyr Davydiuk4 1Bohomolets National medical university, Kyiv, Ukraine, 2Bukovinian State Medical University, Chernivtsi, Ukraine, 3Shupyk National Medical Academy of Postgraduate Education, Kyiv, Ukraine, 4National Pirogov Memorial Medical University, Vinnitsa, Ukraine. Aim: To explore the prevalence of mosaicism in 11 unexplained cases of FAP and to evaluate the impact of somatic testing on the diagnostic yield. With these findings, brittle cornea syndrome was thought as the most accurate diagnosis and PRDM5 gene sequencing revealed a novel c.177+1G>A variant in homozygous state. Information regarding HRR genes status in patients with PC is useful to target treatments (PARPi) or to the eligibility for clinical trials. Introduction: Pleiotropic variants, i.e. those that affect more than one trait, have been found to be abundant in the human genome. Here we present three CS mothers who experience preeclampsia when carrying affected CS fetuses. Results: We identified 118 new paralogous sequence variants and 80 gene conversion events that shaped the diversity of P6 arms during recent human history. Beligni: None. Results: Diagnostic yield of type-IV-collagen-related nephropathy classified as AS compared to TBMN was significantly different (65% vs. Index 4 was diagnosed with CF after pulmonary infections, pathologic SC and compound heterozygosity for F508del and p.(Ala1319Glu). DNA methylation level of promoters of five genes (ANKRD53, GATA3, CALCB, TRPV6, and SCL13A4) was analyzed in detail using targeted bisulfite massive parallel sequencing in the chorionic villus trophoblast of 22 miscarriages with trisomy 16 and 10 induced abortions. This case highlights the relevance of mosaicism even for late onset cancers and the importance of the teamwork between oncology, anatomopathology and clinical genetics specialists in a modern facility. Conclusions• We present a new workflow to transfer sheared gDNA using Echo liquid handling technology.• The gDNA was transferred from Echo qualified tubes with comparable results to traditionalmethods.• We can further miniaturize the assay as the Echo 655T can accurately, precisely andreproducibly transfer 2.5 nL drops. We discuss how CMA-SNP data can contribute to understand the mechanism of aneuploidy. Williams3, Ashley Kuhl3, Jessica Scott Schwoerer3, Harold E. Huang: None. Grochowski 1, Lorraine Potocki1, Anna Lindstrand2, Claudia M. P12.129.A Specific phenotype of germline MET mutations in papillary renal cell carcinoma type 1: about a large french series of 158 patients Molka SEBAI 1, David TULASNE2, Sandrine M. Koltsova1, Anna A. Materials and methods: Colon tissue collected from HSCR patients (n =5) and controls (n = 5), was used to isolate ENS cells by enriching for the neuronal marker p75NTR with magnetically activated cell sorting. Desplas: None. We have shown that the PADI4 genotypes (rs11203367, rs2240340, rs11203366, rs874881) are significantly associated with the baseline levels of DAS28-CRP, HAQ-DI, CDAI, genotypes IL23R (rs7530511), TNFRSF1A (rs748004, rs2228144) with the level of ACPA, the genotypes DHODH (rs3213422), MTHFR (rs180113) with the concentration of CRP, and the genotypes IL2RA (rs2104286), IRAK3 (rs11541076) and IL4R (rs1801275) with the level of RF. Results: In both symptomatic sisters, we found a homozygous missense variant in exon 6 (c.964G>A), resulting in an amino acid exchange (p.Val322Met). Lanko: None. P09.014.C Genomic data suggests the involvement of TLR5 variants in modifyingthe risk for Alzheimer's disease Dragomira N. Yovinska: None. de Boer, Kim A. P09.044.A When two is one -a case of homozygous mutation in STXBP1 gene as a result of single-parent disomy Dorota Hoffman-Zacharska 1, Anna Winczewska-Wiktor2, Marta Smyk1, Paulina Gorka-Skoczylas1, Karolina Kanabus1, Barbara Steinborn3 1Department of Medical Genetics, Institute of Mother and Child, Warsaw, Poland, 2Department of Developmental Neurology, Poznan University of Medical Sciences, Poznan, Poland, 3Department of Developmental Neurology, Poznan University of Medical Sciences, Warsaw, Poland. A plethora of novel mutations was documented further expanding the genetic heterogeneity. To date, ten live-born and seven prenatal cases with either maternally inherited or de novo variants in NONO were reported in fourteen families. coli, from urine and blood for K. Materials and Methods: Because these studies were limited in size, we screened the exome data of our Male Reproductive Genomics (MERGE) cohort of currently 1,003 men with various infertility phenotypes and some fertile controls for variants in TEX13B. Methods: NGS and Sanger sequencing. Motolese: None. Myllykoski: None. Results: In 2282del4/wt IV individuals, the distributions of wild-type, heterozygous and variant homozygous genotypes were: rs1801133 — 0.29:0.71:0.00; rs1801131 — 0.53:0.47:0.00; rs1805087 — 0.70:0.24:0.06; rs1801394 — 0.23:0.53:0.24. This altered interaction leads to posttranslational overmodification of type I procollagen, with increased glycosylation and/or hydroxylation of lysine and proline residues as shown by mass spectrometry. It is highly expressed in the ventricular zone of the brain during embryonic development. Trabanelli: None. Although proband's parents were not available for the genetic analysis, this case highlights the growing relevance of genetic testing for this condition. It arises due to abnormalities in the anterior chamber angle development, that obstructs aqueous outflow in the absence of systemic anomalies or other ocular malformations. Botezatu: None. Cardona-Londoño2, Karla A. The development of technologies like Next Generation Sequencing (NGS) has revolutionized the practices of the Medical Genetics. V.S. Ramakumaran: None. Lipilkina: None. Laurynaitiene: None. It is usually initiated by clinical genetics providers, and the diagnostic yield is generally between 10 and 12%. Uslu1, Nermin S. Barros-Campos: None. He has distinctive features consistent with a Rasopathy, but not typical of CS. Le Maréchal: None. Variant alleles in pharmacogenes are responsible for adverse drug reactions in relation with chemotherapy, antiemetic or pain treatments. Results: We observed a significant decrease of Aβ1-40 levels in the extracellular media of SYS fibroblasts compared to both PWS patients and controls. Results: GAPDH was the most stable reference gene and protein. Fundings: JPND-PERADES, FRM-DEQ20170336711, Fondation Alzheimer ECASCAD, FRM-ARF201909009263, GMAJ PHRC-2008/067, CNRMAJ C. Molecular mechanisms of pain are complex and difficult to entangle, but important to understand to treat pain disorders. Materials and Methods: We performed a pilot study analyzing exomes of 90 ischemic stroke cases with extreme functional recovery scores three months after stroke (modified Rankin Scale (mRS) 0-1 vs 4-5), matched by age, gender and stroke severity, to select target genes involved in functional outcome. Palombi: None. Kubisch: None. Results: In the association analyses of genetic variants and progressive disease, SLC7A8 rs1884545 and SLC7A8 rs8013529 were significantly associated with progressive disease and were independently validated in the validation cohorts (meta-analysis: OR 0.22 [0.07-0.63], P = 0.005 and OR 0.19 [0.06-0.55], P = 0.002, resp.). Carley: None. Vendramini- Pittoli: None. Tarani: None. Guipponi: None. Both of them were from non-consanguineous parents with no significant family history. Castro2, Juan Ramon Gimeno Blanes1 1Inherited Cardiac Disease Unit. Dunlop: None. Results and discussion: The most frequent drug response associated polymorphisms were discovered in CYP2D6 (c.506-1G>A) and CYP2B6 (c.516G>T), followed by CYP2D6 (c.100C>T), CYP2B6 (c.785A>G) and CYP2C9 (c.1075A>C). Apetrei: None. Because some somatic expansions beyond a particular CAG-length are likely to cause cellular dysfunction, further studies in tissues that drive HD neurodegeneration are warranted, especially for alleles close to the pathologic boundary. M.H.S. Roeffen: None. The mother is heterozygous for c.283G>C(Ala95Pro). H.D. Schrøder: None. Crosby1, Emma L. L.M. Morgado: None. To date, only PAX6, SLC38A8 and AHR are known to be associated with Isolated Foveal Hypoplasia (FVH), but few patients undergo extensive clinical and molecular investigations. Of note, we reported discordant phenotype in twin female patients 5& 6. Grant: BIND EU Grant N. Here, we describe a Tunisian pedigree in which a young female was diagnosed as having familial bilateral cervical ribs. Favero: None. One DBD-variant (p. The 3'UTR LDLR variants were generate into the expression vector LDLR_NM_000527-Human-cDNA-luciferase reporter by site-directed-mutagenesis and transfected in cell line HepG2. Sørensen1,2, Niels Grarup1, Mario García Ureña1, Dmitrii Borisevich1, Jean-Michel Oppert3, José Alfredo Martínez Hernandéz4,5, Ellen Blaak6, Tuomas Oskari Kilpeläinen1 1Novo Nordisk Foundation Center for Basic Metabolic Research, Copenhagen N, Denmark, 2Department of Public Health, Section of Epidemiology, University of Copenhagen, Copenhagen, Denmark, 3Nutrition Department, Pitie-Salpêtrière Hospital, Assistance Publique Hôpitaux de Paris, Sorbonne University, Paris, France, 4Department of Nutrition, Food Sciences, and Physiology, Center for Nutrition Research, University of Navarra, Pamplona, Spain, 5Centro de Investigación Biomédica en Red Fisiopatología de la Obesidad y Nutrición, Instituto of Health Carlos III, Madrid, Spain, 6Department of Human Biology, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, Netherlands. PLK3-rs12404160 AA genotype was associated with higher risk in male population (OR = 3.55, 95% CI = 1.26-10.04, P = 0.015). Miseta: None. Knaus: None. Photos of the patient and measurements of NAD metabolites will be provided. Results: Patients and carriers had lowered PPi levels (respectively ±51% and ±78% of controls; P A (p.Gly375Arg) was detected in the KCNMA1 gene. Kazakov: None. It is mainly a non-immune hydrops fetalis (NIHF). Bos4, Encarna B. Pinna: None. Latchford10,11, Monique E. For example,our initial results suggest that there is evidence of balancing selection in TARBP1, a gene involvedin the development of AIDS. Introduction: Large datasets of whole-genome sequencing (WGS) require fast read alignment and variant calling pipelines. P25.012.C Incidence and severity of COVID-19 in rare disease populations Zoe C. In certain situations (genetic counselling in particular), a clinical examination is not required. This study focuses on copy number variants (CNVs) and whether the diagnostic yield might be improved by routine CNV detection. Guerra: None. Based on this, 15 patients were diagnosed as having CSNB and one presenting Retinitis pigmentosa (RP). Zeman: None. L. Grenda: None. Esperón-Moldes, Rosario Ferrer-Avargues, Alfonso Andújar, Tania Otero-Rodríguez, Natalí Riva, Vanesa Felipe-Ponce, Elena Mesa-Rísquez, Isabel Sánchez-Guiu, María D. de Lange: None. The resulting TR profile is comparable to other previously published European cohorts. Palmieri: None. Consultant/Advisory Board; Modest; Advaxis, Eisai, MSD belgium, Roche NV, GenMab, F. Introduction: Mitochondrial dysfunction is well-known to co-occur with Type 2 diabetes (T2D); a reflection of this is the fact that multiple T2D drugs and treatments target the mitochondria. The second family (F2) displayed 2 sisters affected by endometrial cancer and one brother with colon cancer. Interestingly, these two patients share similar facial features with epicanthic folds and cupped ears. Olivier: None. Efinska-Mladenovska: None. Introduction: Pain management for nociceptive musculoskeletal pain (NMP) follows analgesic ladder, starting from nonsteroidal anti-inflammatory drugs (NSAID), followed by weak or strong opioid until pain is under control. We want to thank the "CERCA Programme" from the Autonomous Catalan Government. This suggests that the deletion is a frequent cause of monogenic hearing impairment in the Netherlands, with potentially 8,000 affected individuals, and a significant cause of hearing impairment in neighboring countries. At the molecular level, the patient has a homozygous biallelic MYH mutation at the exon 13 of the gene: the MUTYH c.1185_1186dupGG variant resulting in a premature termination of the protein. Režen: None. The targeted sequencing of 197 genes was used for tumor-derived ctDNA analysis by next generation sequencing (NGS). Topologically associated domains (TADs) are disrupted by the inversion. Conclusions: We report a patient affected by 3MC syndrome who, besides typical phenotypic signs, presents a patent ductus arteriosus, never described in association to COLEC10 before. Conclusions: There appear to be differences in cerebral manifestations across genes, but this may be due to age and other biases inherent to case reports. The mother has short stature (-2.5SD), a dysplastic mitral valve with mild insufficiency, and has previously been treated for supraventricular tachycardia. N.V. Balinova: None. Vergani: None. Paulin: None. Marcos Rodriguez: None. Autopsy confirmed ultrasound findings and revealed additional features/malformations like hydrocephalus, hypertelorism, cleft lip and palate, bilobar lung, agenesis of the diaphragm, polysplenia, anal atresia, syndactyly of fingers and toes, and broad distal phalanges. Cancer penetrance is unknown, which complicates the development of surveillance and prevention guidelines. Cytogenetic testing involves 2-3 methods including karyotyping, a panel of fluorescent in situ hybridization (FISH) probes, and chromosomal microarray. L.I. Petrova: None. Literature Review: review of ID cases caused by DDX3X variants and 3q29 duplications to compare their genetic and phenotypic spectra vs. Versleijen-Jonkers1, Melissa H. The aim of this work was to identify the CNA-associated breakpoints in a large series of head and neck squamous cell carcinomas (HNSCC) and correlate them with clinical data. The blood RNA was available for 911 individuals and the blood DNA for 198 individuals. Smooth muscle cells were the second cluster in terms of somatic mosaicism frequency (13.5%). Conclusions: Independent CeD-susceptibility loci were associated with distinct phenotypes, suggesting that genetic factors play a role in determining the disease presentation. Background: Wilms tumor (WT) is the most common childhood renal tumor, associated with (epi)genetic predisposing factors including Beckwith-Wiedemann Spectrum (BWSp) and WT1-related syndromes. Moslerová: None. Montejo-Gadea: None. Despite considerable progress in sequencing and bioinformatics approaches, they remain often overlooked due to their balanced nature and mapping issues. The samples with a distance score lower than six were interpreted as microsatellite stable (MSS); whereas the values between six and fourteen indicated microsatellite instability with low confidence (MSI-LC). P24.015.B Genetic variability of 6p22.1 in sepsis susceptibility: a fine mapping association study of the HLATamara Hernandez-Beeftink1,2, Itahisa Marcelino-Rodriguez1,3, Eva Suarez-Pajes 1, Megan L. C.P. Lanting: None. Polyzou: None. Also DiGeorge syndrome was excluded by multiplex ligation-dependent probe amplification (MLPA). As part of the broader Sudanese neurogenetic project, we explored the genetics underlying the HA in a cohort of 11 families. Patient B has prominent forehead, hypacusis, generalized muscular atrophy and lower limb paresis in early childhood. Furthermore, it has been shown very recently that ARID2 haploinsufficiency is associated with enhanced RAS-MAPK activity. The underlying molecular causes for the observed ID phenotype is at present not well understood. P15.044.D A fully automated workflow for SARS-CoV2 RNA detectionJethary Rader1, Kinnari Watson1, Han Wei 2 1Opentrons Labworks Inc, Brooklyn, NY, USA, 2Beckman Coulter Life Science, Indianapolis, IN, USA. Fleischer: None. Almannai: None. These differences have an impact on the way ethical issues emerge, and questions about the meaning of health, illness and disability, the scope of public health interventions, social inclusion and exclusion as well as reproductive choice are approached in each country. P09.015.D Analysis of pathogenic variants in Alzheimer's disease related genes in cases, healthy young controls and centenarians Sena Karachanak-Yankova 1,2, Dimitar Serbezov1, Lubomir Balabanski1,3, Marta Mihaylova1, Dragomira Nikolova1, Mihail Ganev1, Desislava Nesheva1, Zora Hammoudeh1, Blaga Rukova1, T Dekova2, Diyana Belezhanska4, Shima Mehrabian4, Mariya Petrova4, Latchezar Traykov4, Savina Hadjidekova1, Draga Toncheva1 1Department of Medical Genetics, Medical Faculty, Medical University-Sofia, Sofia, Bulgaria, 2Department of Genetics, Faculty of Biology, Sofia University "St. Kliment Ohridski", Sofia, Bulgaria, 3Gynecology and assisted reproduction hospital "Malinov", Sofia, Bulgaria, 4Depatment of Neurology, UH "Alexandrovska", Medical University-Sofia, Sofia, Bulgaria. Introduction: Homologous recombination deficiency (HRD), caused in 40-50% of cases by BRCA1/2 pathogenic variants (PVs), is a predictive biomarker for the response of different tumors to PARP-inhibitor therapy and, in epithelial ovarian cancer (EOC), also considered predictive for sensitivity of platinum-based therapies. Methods: We performed exome sequencing in a multiplex family previously reported by Hilger et al. Rousselet: None. Van Dooren: None. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Modest; qGenomics, ISGlobal. In the plasma of sinistral side at the 5th minute we identified two miRNAs: hsa-miR-7-5p and hsa-miR-375-3p that were highly upregulated compared to peripheral blood. Brand: None. C.T.R.M. Stumpel: None. One patient had a deletion at NRXN1 and six patients (9.7%) presented variants of unknown significance. The male with T315I mutation has 79 years old and had been under the therapy for 11 years. Proband, 7 years old boy, was diagnosed with unclassified epileptic encephalopathy but with features of Lennox-Gastaut syndrome. Powis: A. Armour: None. Hundreds of genes are associated with MDs and genetic diagnosis in clinical practice may end up being a cumbersome odyssey. Mutations in these genes may occur in cases with optic atrophy "plus", and they must be considered during the diagnostic process. Views on including the Clinical Management section were mixed with 75% of respondents agreeing to inclusion. We present the spectrum of abnormalities in SHFM1 cases that depends on the 7q21.2-q21.3 aberrations breakpoints, deletion size and its gene/regulatory elements content. This study aims to identify the shared differentially expressed genes (DEGs) involved in pathogenesis of COPD in blood and lung tissue. The second microdeletion,7.17Mb,encompassed 51 OMIM-genes including the SHANK3 in 22q13.2q13.33(43996288_51169045)(GRCh37/hg19).The 22q13 microdeletion or mutations of the SHANK3 are associated with psychomotor and speech delay.Accompanying features of the case excluded for Beckwith-Wiedemann Syndrome were large for gestational age,macroglossia,renal anomalies, asymmetric growth could due to the impact of other deleted genes.The third case displayed 0.3Mb deletion in 7p15.2(26,938,809_27,262,849)(GRCh37/hg19) harboring the HOXA13. Perez de Nanclares: None. Exome sequencing (ES) is a powerful tool for identifying disease-causing single nucleotide variants (SNVs) and small indels. Conclusion: We didn't find another case reported with this transocation. K.I. Anoshkin: None. Background: Proteoglycans (PGs) are complex macromolecules consisting of a core protein and glycosaminoglycan (GAG) side chains. A standart nomenclature has been developed to describe each of types of abnormality found in human chromosomes. D.J. Turner: A. Pathway analysis of these gene sets reveals the transcription factors and chromatin remodelers involved in this process. P08.002.D Refining the phenotype and expanding the genotype of Xia-Gibbs Syndrome (OMIM #615829) Ana Teresa Serrano Antón 1,2, María José Sánchez Soler1,2, Mary Ballesta Martínez1,2, Vanesa López González1,2, Lidia Rodríguez Peña1,2, Encarna Guillén Navarro1,2 1Sección de Genética Médica. This case seems to confirm that gain of function of OVOL2 causes PPCD1. Depending on the genes involved, patients with duplications in this region may be categorized into either class I or class II. AlSayed: None. P06.017.B Glycogen Storage Disease diagnosis with Clinical Exome Sequencing that has CNV detection capabilitiesBülent Uyanik1, Melike Ersoy2, Sezin Canbek 3 1Bezmialem Vakif University Faculty of Medicine Medical Genetics Department, Istanbul, Turkey, 2Bakirkoy Dr Sadi Konuk Research and Education Hospital, Istanbul, Turkey, 3Umraniye Research and Training Hospital Medical Genetics, Fatih, Turkey. The remaining breakpoints were located in intergenic regions. P13.013.B A novel synonymous-predicted variant in exon 1 of GNAS gene results in a cryptic splice site and causes pseudohypoparathyroidism type 1A and pseudopseudohypoparathyroidism in a French family Andreea Apetrei 1, Arnaud Molin1, Nicolas Gruchy1, Manon Godin1, Claire Bracquemart1, Antoine Resbeut1, Gaëlle Rey2, Gwenaël Nadeau2, Nicolas Richard1 1Department of Genetics, CAEN, France, 2Department of Genetics, Chambéry, France. This study aims to dissect the deeper biological understanding of pathogenetic mechanisms of MS through combinations of human genetics association data and network biology approaches. Electropherograms were generated by Asuragen's prototype AmplideX® CFTR PCR/CE assay using cell lines, blood samples, and synthetic constructs across four CE instruments and different extraction and assay conditions. Corominas: None. Their presence might induce fertilization defects or embryo development failure in oocytes or preimplantation embryos, respectively. H.G. Brunner: None. Both missense variants were classified as VUSs (PM1, PM2, PP3 and PM1, BP4 respectively). Three of the five genes (CEP104, CROCC and NEK1) belong to the ciliary gene family. Cross3, Simon Lam1, Gaurav V. The MVMR reveals that tissue partitioned variants have distinct biological contributions, with brain-regulated BMI driving the effect on outcomes such as coronary artery disease P = 0.009; OR = 1.52; 95%-CI:1.11-2.08) and type-2 diabetes (P = 0.0007; OR:2.66; 95%-CI:1.5-4.7), whereas adipose-regulated BMI was responsible for the effect on osteoarthritis risk (P = 0.01; OR:1.86; 95%-CI:1.16-2.98). Yalcin: None. Consultant/Advisory Board; Modest; Celgene, Roche, Sanofi/Genzyme. Materials and Methods: From March 15 through December 31 2020, all scheduled visits were evaluated. Clean-up kits are a pivotal part of the NGS process. Halloun: None. This study investigates whether PacBio HiFi sequencing on a Sequel II System (Pacific Biosciences) allows for generating long, high quality reads with full phasing, supporting reliable and unambiguous HLA typing. Results: We observed that three CF patients (homozygotes or compound heterozygous for a class I-II) with TT genotypes had failure to thrive, chronic bronchopulmonary infection, bronchiectasis and pancreatic insufficiency. Fokstuen: None. Casas-Alba: None. An alternative approach based on the analysis of individual profiles to search for Stochastic Epigenetic Variants (SEVs) identified an increased number of SEVs in OAVS subjects compared to controls. The proportion of patients with vomiting episodes post-chemotherapy differs between ultra-metabolisers for CYP2D6 and normal metabolisers (40% vs 16%). Morgan, Sian Corrin All Wales Medical Genomics Service, Cardiff, United Kingdom. Introduction: Baraitser-Winter cerebrofrontofacial syndrome (BWCFFS) is a rare multisystem developmental disorder characterized by distinctive craniofacial features, intellectual disability, ocular colobomata, hearing loss, short stature, brain malformation, epilepsy, structural anomalies of palate, heart and kidneys. Moorthie: None. Results: Participants described barriers related to accessing screening services or high quality LFS-related care, and inadequate financial resources for screening-related expenses. Genetic analysis provides determining of diagnosis in cases with suspected HPP. Conclusions: A pathogenic mtDNA mutation does not modify the mtDNA metabolism in human cleavage-stage embryos, suggesting the absence of negative selection at this stage. It integrates information from key epigenetic resources and is included as a native regulation track at the UCSC genome browser. All tested GPI-APs were unchanged on granulocytes whereas FLAER and CD73 levels in fibroblasts were decreased. Wapstra: None. We detected novel transcript-specific markers including ABI3BP, PTPRE, PRDX1 and GADD45 found in both transcript-level and splicing analyses. Latif Khan: None. 4) There was no method for calculating in house variant frequency. Considering the above, it is of significant importance to stratify breast cancer patients using predictive biomarkers in order to maximize the efficacy of TRAIL targeting therapies. M.C.J. Jongmans: None. This syndrome affects about 1 in 1,000,000 births. Ciliberto: None. Zamani Esteki: None. As over half of the consultees required extended counseling beyond the basic explanation, assigning sufficient time for the consultation is important. Marí: None. Guerini: None. Germline variants were classified according to ACMG guidelines. Long term complications includes also low bone mineral density. Nowé: None. Pacio-Miguez: None. Hansikova: None. Macho Carballido: None. Result: 46,XX,r(22)(p11.2q13), Phelan McDermid syndrome, recommendations for the rehabilitation of the child were given. Bult, The Mouse Genome Informatics Staff and Software Team The Jackson Laboratory, Bar Harbor, ME, USA. She had generalized acanthosis nigricans (neck, axillae, elbows, groins and knees), BMI 21.38kg/m2, and reduced fat in the face, upper and lower extremities. We hypothesize that in the absence of functional MESD, WNT signaling in osteogenic cells is blocked. M.Y. Chan: None. Aarskog-Scott syndrome (ASS) or facio-digito-genital dysplasia (OMIM#305400) is a rare X-linked inherited disorder caused by pathogenic variants in the FYVE, RhoGEF, and pleckstrin homology domain-containing protein 1 (FGD1) gene. Genetics Department, Hospital Universitario La Paz, IdiPAZ, Madrid, Spain.of dislipemias of genetic origin and metabolic diseases, IdiPAZ, Hospital Universitario La Paz, Madrid, Spain., Madrid, Spain, 6Preanalytic Section. In the literature, 6 cases of WT (0.12%) and 4 cases of other cancers have been reported out of 483 PIK3CA patients, carying p.His1047Leu/Arg in particular (15 patients with WT, 40 with other cancer out of 820 patients with no molecular confirmation). Moghaddasi: A. Results: 7 patients and 2 healthy relatives presented a known pathogenic variant (PMVK c.412C> T; p.R138*), and 6 patients and 4 of their relatives presented a synonymous variant (PMVK c.147A>G; p.E49=). Sobczyńska-Tomaszewska: None. Sokołowska: None. Pérez-Sánchez: None. Comparison with previously described "classic" NF1 cohorts showed a significantly higher proportion of symptomatic spinal neurofibromas, dysmorphism, learning disabilities, malignancies, and skeletal and cardiovascular abnormalities in the NF1-deleted group. We aim to assess ovarian cancer characteristics as predictors of BRCA1/2 variant pathogenicity, for inclusion in the Multifactorial model and as clinical data points using the American College of Medical Genetics and Genomics and Association for Molecular Pathology (ACMG/AMP) quantitative evidence system. A.H. Abd Ali: None. P10.023.C Dystrophin isoforms transcription heatmap in human adult control brain areas Maria Sofia Falzarano 1, Rachele Rossi1,2, Martina Mietto1, Fernanda Fortunato1, Rita Selvatici1, Pietro Spitali3, Federica Montanaro2, Francesco Muntoni2, Alessandra Ferlini1,2 1Unit of Medical Genetics, Department of Medical Sciences, University of Ferrara, Ferrara, Italy, 2The Dubowitz Neuromuscular Centre, UCL Great Ormond Street Institute of Child Health, London, United Kingdom, 3Department of Human Genetics, Leiden University Medical Center, Leiden, Netherlands. Here we describe the results from the last 5 years of our strategy. Physical examination showed oral leukoplakia, thin/sparse hair, lacy reticular hyperpigmentation on left axillary region and right hemithorax; cranial MRI showed cerebellar hypoplasia. P12.154.B Using FFPE tissue from non-mucinous epithelial ovarian cancer patients to detect germline variants José Luis Villanueva-Cañas 1, Míriam Potrony2,3, Adela Saco4, Ricard Isanta1, Vanesa Lopez1, Victor Pastor1, Elena Gonzalvo Mallón4, Mireia García Gerona4, Lorena Moreno5, Belén Pastor6, Eduardo González7, Bárbara Adamo5, Lydia Gaba8, Aurora Sánchez2, Pedro Jares1,4, Joan Antón Puig-Butillé1,2 1Molecular Biology CORE Laboratory, Hospital Clínic de Barcelona, Barcelona, Spain, 2Biochemical and Molecular Genetics Department, Hospital Clínic de Barcelona, Barcelona, Spain, 3Centro de Investigación Biomédica en Red en Enfermedades Raras, Instituto de Salud Carlos III, Barcelona, Spain, 4Pathology Department, Hospital Clínic de Barcelona, Barcelona, Spain, 5Gastroenterology Department, Hospital Clínic de Barcelona, Barcelona, Spain, 6Medical Oncology, Hospital Clínic de Barcelona, Barcelona, Spain, 7Obstetrics and Gynecology Department, Hospital Clínic de Barcelona, Barcelona, Spain, 8Medical Oncology Department, Hospital Clínic de Barcelona, Barcelona, Spain. Twenty (80%) patients had cardiac diseases, often mitral valve defects and/or cardiomyopathy. Zeinali: None. G.A. Bazykin: None. Tsezou: None. The diagnosis was confirmed by the 3D-CT in all 17 cases when performed (52%), and/ or by molecular screening after amniocentesis (43%). P19.003.C Association of archaic introgression tracts to modern human facial features Pierre Faux 1, Betty Bonfante1, Javier Mendoza-Revilla2,3, Rolando Gonzalez-José4, Lavinia Schüler-Faccini5, Maria-Catíra Bortolini5, Victor Acuña-Alonzo6, Samuel Canizales-Quinteros7, Carla Gallo3, Giovanni Poletti3, Gabriel Bedoya8, Francisco Rothhammer9, Kaustubh Adhikari10,11, Andres Ruiz-Linares1,11,12 1UMR7268 ADES, Aix-Marseille University, Marseille, France, 2Unit of Human Evolutionary Genetics, Institut Pasteur, Paris, France, 3Laboratorios de Investigación y Desarrollo, Universidad Peruana Cayetano Heredia, Lima, Peru, 4Instituto Patagónico de Ciencias Sociales y Humanas, Centro Nacional Patagónico, CONICET, Puerto Madryn, Argentina, 5Departamento de Genética, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, 6Molecular Genetics Laboratory, National School of Anthropology and History, Mexico City, Mexico, 7Unidad de Genomica de Poblaciones Aplicada a la Salud, UNAM-Instituto Nacional de Medicina Genómica, Mexico City, Mexico, 8GENMOL, Universidad de Antioquia, Medellín, Colombia, 9Instituto de Alta Investigación, Universidad de Tarapacá, Arica, Chile, 10School of Mathematics and Statistics, The Open University, Milton Keynes, United Kingdom, 11Department of Genetics, Evolution and Environment, and UCL Genetics Institute, University College London, London, United Kingdom, 12Ministry of Education Key Laboratory of Contemporary Anthropology and Collaborative Innovation Center of Genetics and Development, Fudan University, Shanghai, China. Results: We demonstrate that GDAP1 participates in basal autophagy and its depletion affects autophagosome biogenesis and membrane trafficking from MAMs. GDAP1 also participates in lysosome maturation by interacting with PYKfyve, a pH-dependent kinase. Candidate variants detected could be the genetic factors that aggravate the malformation in siblings and are being investigated for possible relations to pathways regulated by BTRC. P03.035.C A clinical case of patient with cholestatic liver disease due to mutations of the MYO5B Tamara Yurievna Lesnichenko 1, Natalia Alexandrovna Semenova2, Olga Nikolaevna Ivanova2, Elena Anatolievna Kamenec2, Ekaterina Yurievna Zakharova2 1Federal State Budgetary Educational Institution of Further Professional Education "Russian Medical Academy of Continuous Professional Education" of the Ministry of Healthcare of the Russian Federation, Moscow, Russian Federation, 2Federal State Budgetary Scientific Institution "Research Centre for Medical Genetics", Moscow, Russian Federation. Chelysheva3, Anna G. Rideau: None. Cyclophilin B (CyPB), encoded by Ppib, functions as a procollagen prolyl 3-hydroxylation complex component (P3H1/CRTAP/CyPB) and independently as the major peptidyl-prolyl cis-trans isomerase (PPIase) catalyzing collagen folding. Araki: None. Moebius syndrome (MBS; OMIM #157900) is a rare congenital disorder characterized by nonprogressive facial and ocular abduction paralysis, and impairment to the facial (cranial VII) and abducens (cranial VI) nerves, respectively, possibly due to hindbrain defects. Ownership Interest (stock, stock options, patent or other intellectual property); Modest; Tailor Bio. Ejarque-Vila: None. Hennies: None. Results: We describe four males, ages between 7 and 24 years, born to healthy non-consanguineous parents. Lawrence: None. The mutated GluN2B correctly interacts with wild type GluN2B and GluN1 subunits forming functional receptor. Patient diagnoses have included monogenic auto-inflammatory disease, complement deficiency, Fabry disease, XXX syndrome, camptodactyly-arthropathy-coxa vara-pericarditis syndrome and arthropathy secondary to tufting enteropathy. L.S. Chitty: None. P04.032.A Aarskog-Scott syndrome: case report and updated-review Marta Spodenkiewicz 1, Gauthier Loron2,3,4, Céline Poirsier1, Francesco Laconi5, Marie Massier1, Perrine Venot2, Clémence Jacquin6, Lucas Hérissant1, Emilie Landais1, Martine Doco-Fenzy1,7,8 1Service de génétique, CHU de Reims, Reims, France, 2Service Pédiatrie B, CHU Reims, Reims, France, 3Faculté de médecine, Reims, France, 4CReSTIC/ EA3804, Reims, France, 5Service de chirurgie Pédiatrique, CHU de Reims, Reims, France, 6CHU Reims genetics Unit, Reims, France, 7SFR CAP SANTE, UFR de médecine, Reims, France, 8EA3801, Reims, France. In contrast, VKORC1 was found to be functionally, highly polymorphic with 53.7% of Saudi individuals harbour variants that are predicted to result in decreased activity and 31.3% of the population having variants leading to increased metabolic activity. Overall, 280 consecutive families were included. Polimeni: None. We have developed the Loss-of-Function ToolKit (LoFTK), which allows efficient and automated prediction of LoF variants from both genotyped and sequenced genomes. Material and methods: The proband is a girl aged 6 years. Adhikari: None. FKBP22 acts as a molecular chaperone involved in the folding and quality control of collagen molecules (among which types III and VI collagen). Here we introduce HD Hub, a centralized database with hundreds of thousands of heritability and genetic correlation estimates, estimated using HDL based on harmonized summary association statistics for complex traits from LD Hub and UK Biobank (UKBB). Bruque 2 1Centro Nacional de Genética Médica - ANLIS- Malbrán., CABA, Argentina, 2Hospital de Alta Complejidad- SAMIC - El Calafate, El Calafate, Santa Cruz, Argentina, 3INIGEM, CONICET / Cátedra de Genética y Biología Molecular, Universidad de Buenos Aires, CABA, Argentina, 4CEGYR, Medicina Reproductiva y genética, CABA, Argentina, 5Departamento de Fisiología, Biología Molecular y Celular. P09.125.B Three novel heterozygous variants in the MACF1, POLA1 and TOP3B genes: a new phenotype associated with the TOP3B gene? Peptidyl citrulline is a target antigen of anti-citrullinated peptide antibodies (ACPAs), and only PADs (translated protein from PADI genes) can provide peptidyl citrulline via modification of protein substrates. Osteogenesis imperfecta (OI) is a collagen-related bone disorder, which is caused by either dominant mutations in collagen, or recessive defects in genes encoding collagen-interacting proteins. Cui: None. Patients with BRPS require multidirectional care with the individualization of the learning process. It is a muscle relaxant that selectively blocks the RYR1 channel. Molecular karyotyping showed no genomic imbalance. J.H. Vedovato-dos-Santos: A. Most of the variants were found in genes linked with cancer susceptibility syndromes - 36% (BRCA1, BRCA2, MSH6, RET, PMS2, RAD50, BRIP1, CHEK2) and congenital heart diseases - 33% (DSG2, SCN5A, TNNI3, KCNH2, KCNQ1, TNNC1, TTN). Guignard: None. Materials and Methods: We used gene expression and DNA methylation profiles from 9039 human tumors to generate 16 cancer type classifiers. Consultant/Advisory Board; Modest; qGenomics. Conclusions: Through a rapid and simple workflow, Nanopore technology allows the molecular diagnosis of genomic disorders within 30 minutes to 30 hours time-frame. 2) Scientists analysing the case could not modify filtering parameters to investigate cases in more detail. In those QF-PCR analysis identified aneuploidy/triploidy in 21.42%. Introduction: Kabuki syndrome 1 and 2 (OMIM #147920 and #300867) characterized by distinctive facies, learning disability and multiple congenital anomalies are caused by pathogenic mutations in the lysine-specific methyltransferase 2D (KMT2D) and lysine-specific demethylase 6A (KDM6A) genes respectively. Lopez-Escamez: None. Doheny: None. Here, we report three affected individuals (two siblings and one cousin) with short stature, microcephaly, severe intellectual disability, developmental delay, hypotonia, facial dysmorphism and microphthalmia, from a Pakistani consanguineous family in which we have identified homozygosity for p.(Arg350Pro) in the CDC25B gene (Genbank NM_021873.3) that segregated with the disease phenotype. Salcedo-Cánovas: None. van den Wijngaard: None. Gallego: None. For the remaining 9, the second variant modulated the phenotype. We decide to perform DMD MLPA test for her. Galinier: None. Analysis of the patients` cDNA showed that c.2727C>T variant causes cryptic donor splice site (DS) activation and 74 b.p. deletion in NPC1 exon 18. M.L. Quintanilla: None. While increased access to testing should be celebrated, the use of first-line exome and genome testing makes variant interpretation a key bottleneck, as highly skilled analysts are not experts on all genes/disorders encountered. Background: Orofacial clefts represent ~30% of all congenital malformations being 30% of cleft lip with or without cleft palate and 50% of cleft palate cases syndromic. Pignataro: None. All index cases had the following: (1) moderate to severe intellectual disability (ID) (intelligence quotient [IQ]/developmental quotient [DQ] ≤55); or (2) mild to moderate ID (IQ/DQG the most frequent RPGRIP1 disease allele (8/60, 13%) in our cohort. Peter P. Andreea C. Patients may have combined dysmorphic features, intellectual disability, and seizures. In the first ever GWAS of transferrin N-glycosylation, we identified 10 significantly associated loci (P C; p.(Asp243His), probably impairing demethylase activity. Introduction: Intellectual capability is one of the most socially significant characteristics. P08.052.B EIF3F-related neurodevelopmental disorder: refining the phenotypic and expanding the molecular spectrumUlrike D. According to the latest data, variants of IL-6 and VDR genes which encode the relevant components of the immune system can affect on the pathogenesis of this disease. Conclusion: Genetic testing has become a first line test in epilepsy. David: None. Barysenka: None. H.M. Jeffery: A. Introduction: "Type-IV-collagen-related nephropathy" describes a spectrum of hereditary hematuric diseases comprising Alport syndrome (AS) and (milder) thin basement membrane nephropathy (TBMN). Introduction: Whole-Exome Sequencing (WES) experiments analyze DNA sequences from protein-coding genomic regions, where more than 80% of pathogenic and causal variants of Mendelian diseases are located. We identified our candidate gene TAB2 and subsequently sequenced TAB2 in patients with matching phenotypes. NGS of exons of 4800 genes associated with the development of various diseases was carried out, and bioinformatic analysis was performed to predict the potential pathogenicity of variants. Bartolomaeus: None. After genotyping of 120 samples from healthy individuals of yakut origin the frequency of heterozygous carriage were estimated: mutation 4582_4583insT in CUL7 gene -2%, mutation c.5741G>A in NBAS gene-1,6%, c.806C>T in DIA1 gene-2,5%, c.-23+1G>A in GBJ2 gene -2,9%. Klančar: None. Conclusions: Compared to FFPE biopsy material that didn't show any statistically significant correlation, cfDNA has better prognostic properties for predicting patients' OS and disease progression rate. P08.011.A BICRA-based neurodevelopmental disorder: Two additional case reports and computational analysis of facial gestalt Axel Schmidt 1, Tzung-Chien Hsieh2, Alexej Knaus2, Sophia Peters1, Elisabeth Mangold1, Martina Kreiß1, Janbernd Kirschner1, Hartmut Engels1, Peter M. An increase in the concentration of propionylcarnitine, glycine, cystine and Proline was detected in the blood; the presence of methylmalonic acid in the urine. Pembegul Yildiz: None. Hopman: None. Rozet: None. PacBio HiFi sequencing of amplicons generated with NGSgo-MX6-1 results in high-quality, long read sequences of HLA. Ousager1,3, Anja L. P06.036.A A novel homozygous missense mutation in UQCRC2associated with severe encephalomyopathy, mitochondrial complex III assembly defect and activation of mitochondrial protein quality controlDaniela Burska1, Lukas Stiburek1, Jana Krizova1, Marie Vanisova1, Vaclav Martinek2, Tomas Honzik1, Jiri Zeman1, Hana Hansikova1, Marketa Tesarova 1 1Department of Pediatrics and Adolescent Medicine, First Faculty of Medicine, Charles University and General University Hospital in Prague, Prague 2, Czech Republic, 22Department of Biochemistry, Faculty of Science, Charles University, Prague 2, Czech Republic. One of CMS, limb-girdle CMS, is caused by mutations in GFPT1, a gene encoding glutamine fructose-6-phosphate transferase 1. Ethical review and approval University of South Wales [19ET1101LR]. P04.038.C A missense mutation in VAV3 in a familial case of high bone mass Núria Martínez-Gil 1, Diana Ovejero2, Natalia Garcia-Giralt2, Leonardo Mellibovsky2, Xavier Nogués2, Raquel Rabionet1, Daniel Grinberg1, Susanna Balcells1 1Department of Genetics, Microbiology and Statistics, Faculty of Biology, Universitat de Barcelona, CIBERER, IBUB, IRSJD, Barcelona, Spain, 2Musculoskeletal Research Group, IMIM (Hospital del Mar Medical Research Institute), Centro de Investigación Biomédica en Red en Fragilidad y Envejecimiento Saludable (CIBERFES), ISCIII, Barcelona, Spain. Healthcare professionals (HPs) feel a duty towards DTC-GT consumers as patients, yet some feel managing patients with DTC-GT is not an appropriate use of their time, impacts resource allocation and adds to HP workload. Experience of three institutions from the Spanish National Health Service Carmen Ayuso 1,2, Javier Ruiz Hornillos3, Lucia Llanos4, Sandra Zazo5, Lidia Fernández-Caballero1,2, Federico Rojo5, Esperanza García-Molina6, Teresa Escámez6, Encarna Guillen-Navarro7,8 1Department of Genetics and Genomics, IIS - University Hospital Fundación Jiménez Díaz, Universidad Autónoma de Madrid (IIS-FJD-UAM), Madrid, Spain, 2Centre for Biomedical Network Research on Rare Diseases, Instituto de Salud Carlos III, Madrid, Spain, 3Department of Clinical Bioethics, University Hospital Infanta Elena, (IIS-FJD), Madrid, Spain, 4Clinical Research Unit. of hypertrophic - (HCM) /dilated- (DCM), 16 arrhythmic cardiomyopathy (ACM), 20 sudden arrhythmic death (SADS) and 18 sudden unexplained death cases (SUD). P01.100.D Analysis of preimplantation human and bovine embryos with regard to XIST repression on the future active X Melis Atalar Aksit 1, Bo Yu2, Bernard A. Bilateral coronal synostosis was detected on three dimensional cranial computed tomography. Changes in DNA methylation patterns can also be signatures of habit-related diseases, and their study is of medical significance. Belužić: None. Clinical data from a recently published large Spanish cohort of HLRCC (PMID_33167498) was used to assess the clinical phenotype of this founder mutation and to look for genotype-phenotype associations, including 104 individuals with this mutation and 93 individuals carrying other FH pathogenic variants. Research grants: ARRS L3-8203, L3-2622 and P1-0170. Wagner: None. Schwendinger: None. We carried out whole genome bisulfite sequencing (WGBS) of 10 Tibetans (5 from each altitude) and analyzed data in R. Clinical phenotyping, imaging examinations, appropriate genetic and metabolic investigations were offered to children with dysmorphic features/ multiple congenital anomalies. Cravero: None. P01.023.C Three foetuses with Cornelia de Lange diagnosis: prenatal findings and genetic diagnosis Fe Amalia García Santiago 1,2, Elena Mansilla1,2, Eugenia Antolin3, Fernando Santos Simarro1,2, Roberto Rodriguez3, Julian Nevado4,2, Maria Palomares-Bralo4,2, Karen Heath1,2, Rita Maria Regojo5, Carmen Rodriguez-Jimenez6, Isabel Vallcorba6, Angela del Pozo4, Pablo Lapunzina4,2 1INGEMM, Hospital Universitario La Paz, Idipaz, UMDE, Ciberer, Madrid, Spain, 2Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER, U753), Instituto Carlos III, Madrid, Spain., Madrid, Spain, 3Department of Obstetrics and Gynaecology, Hospital Universitario La Paz, Idipaz, UMDE, Madrid, Spain, 4INGEMM, Hospital Universitario La Paz, Idipaz, Ciberer, Madrid, Spain, 5Department of Pathology, Hospital Universitario La Paz, UMDE, Madrid, Spain, 6INGEMM, Hospital Universitario La Paz, Madrid, Spain. As the life span of RD patients has recently increased, an issue of care during transition from pediatric to adult care has arisen. Paternal super-haplogroups H and JT are associated with mild phenotypes, whereas variants with 15%-5% heteroplasmy are associated with severe phenotypes. In particular, hypo-SEMs showed a mean difference between cases and controls about three-fold higher than hyper-SEMs. Moreover, mean SEMs increases in relation to asbestos exposure in cases but not in exposed controls. We obtained no difference in the frequency of CYP1A1, CYP1A2 and GSTP1 between the study and control groups. The exceptional phenomena observed as the coexistence of multiple genetic disorders in the same of the highly inbred families and intra-familial variation in the phenotypic presentations impose challenges on the analysis of the WES data and necessitate larger-scope studies to fully understand the mechanisms underlying Sudanese neurogenetic disorders. Sabbagh: None. Siu 1,5 1Medical Genetics Program of Southwestern Ontario, London Health Sciences Centre, London, ON, Canada, 2Division of Developmental Pediatrics, Department of Pediatrics, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada, 3Family Mental Health Research Institute, CAMH, Toronto, ON, Canada, 4Department of Pathology and Laboratory Medicine, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada, 5Division of Medical Genetics, Department of Pediatrics, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada. Al-Sannaa: None. Future follow-up of literature and databases will determine whether these candidate genes prove to be valid, increasing diagnostic yield even more. Functional studies are recommended to elucidate the risk posed by the GA haplotype for the development of RA. Most applications of these methods were limited to analyzing the autosomal variants, while the X chromosome was often neglected. Mutation c.488G>A (p.Arg163Gln), with the allele frequency 0.004% (ExAc) was classified as a variant of uncertain significance (VUS) (VarSome). Ott Research Institute of Obstetrics, Gynecology and Reproduction, Saint-Petersburg, Russian Federation, 4City Hospital 40, Saint-Petersburg, Russian Federation, 5Diagnostics and Cardiovascular

Surgery Center (Cardiology Clinic) of KHMAO-Ugra, Surgut, Russian Federation. Material and method: 117 patients diagnosed with advanced high-grade serous ovarian cancer were selected for the study based on the criteria of the exceptional response to treatment, i.e. the complete clinical or pathological response to chemotherapy coupled with the disease-free interval of at least 12 months. Klumsathien: None. The aim of the study was to highlight early symptoms and signs in Egyptian patients with MPS and to assess their main clinical features. Chong, Victoria Collins, Emily Lancastle, David Henshall, Blair Wilson, Tim Wilkinson, Kirsty Wilson, Cathie Sudlow, Joanna Wardlaw, Kristiina Rannikmäe University of Edinburgh, Edinburgh, United Kingdom. We also found a new mutation that requires further study of its effect on enzyme function and the pathogenesis of MDS, AML and CML. P07.030.B New "ural" variants of BTK-gene in Russian patients with agammaglobulinemia Svetlana Deryabina 1,2,3, Elena Vlasova4, Irina Tusankina1,2 1The Ural Institute of Immunology and physiology, Ekaterinburg, Russian Federation, 2Federal State Autonomous Educational Institution of Higher Education «Ural Federal University named after the first President of Russia B.N.Yeltsin, Ekaterinburg, Russian Federation, 3Medical Center "Health Care of Mother and Child", Ekaterinburg, Russian Federation, 4Sverdlovsk Regional Children Clinical Hospital, Ekaterinburg, Russian Federation. One viral strain presented a two previously unreported mutation in the ORF14 and nsp3 region, namely p.G50N and p.N1587Y. M.J. Forner: None. Obukhova: None. The WES was performed for a 46,XY SRY positive patient with gonadal dysgenesis. P02.019.D The Fraser-complex pathologic spectrum: Familial cryptophthalmos in two families from GAFSA, TUNISIANouha Bouayed ABDELMOULA, Sonda Kammoun, Fatma Abid Mzid, Saloua Ben Amor, Jamel Feki, Takwa Sammouda, Mouna Rekik Genomics of signalopathies at the service of medicine UR17ES36, Medical University of Sfax, Sfax, Tunisia. Data was then extracted thematically and synthesised to uncover descriptive themes and to generate analytical themes related to barriers and enablers to primary care implementation. Nöthen1, Stefanie Heilmann-Heimbach1 11Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Bonn, Germany, 2Institute for Genomic Statistics and Bioinformatics, University of Bonn, Bonn, Germany. Importantly, a number of other studies have recently been published identifying MNS1 mutations in individuals worldwide with situs abnormalities and/or male infertility. S.M.J. Hopman: None. It corresponds to 14 cases (11 deletions and 3 duplication). Yang: None. Betz1 1Institute of Human Genetics, University of Bonn, Bonn, Germany, 2Givi Zhvania Academic Clinic of Pediatrics, Tbilisi State Medical University, Tbilisi, Georgia, 3Department of Pediatrics, University of Bonn, School of Medicine & University Hospital Bonn, Bonn, Germany, 4Department of Dermatology, University Hospital Freiburg, Freiburg, Germany, 5Institute of Structural Biology, University of Bonn, School of Medicine, Bonn, Germany. Employment (full or part-time); Significant; Quantib BV.. Conclusions: Some older case was diagnosed after grown up. Rollier: None. Because of potential life-threatening complications associated with a diagnosis of HCM, careful investigations of patients are needed, including genetic analysis. A strong suggestion of consanguinity was found in 8.9% of the cases. As a result, many of the published penetrance estimates for neurosusceptibility loci, intellectual disability, schizophrenia and autism are overestimated. Sturm: None. We could also observe CAG length-dependent mosaicism in alleles with 75th percentile were burdened by a significantly worse outcome (Median PFS: 7.8 months, P = 0.0290). The study expands the range of clinical and genetic features of hereditary ophthalmological pathology associated with the ABCA4 gene. Materials and Methods: Mitochondrial bioenergetics were assessed by oxygen consumption rate with a Seahorse XFe96 Extracellular Flux Analyzer. Traditional automation requires commitment to a small set of protocols, necessitating high throughput and batching, to justify the investment of time, space, and capital. In adult male KO mice, failure to complete chromosome synapsis causes meiotic arrest, presumably due to its absence from the SC. 14 TIER-IA variants were confirmed by gold standard method. E.S. Vashukova: None. Segura: None. Three of the findings lead to diagnosis of unsuspected chromosomal disorder and the other three required genetic counselling in first grade relatives at risk with possible further impact on their reproduction. Results: Following a normal CMA result, WES was recommended. Hugel: None. In control group, 103 healthy children and their mothers were included. P09.114.C A biallelic frameshift indel in PPP1R35 as a cause of primary microcephaly Moez Dawood 1, Gulsen Akay1, Tadahiro Mitani1, Jawid M. Discussion: Combining three different strategies, we reduced the risk of methodological biases associated with any single method. The L11 allele p.(Leu21tri) associated with familial combined hyperlipidemia was found in 17 probands with varying phenotypes, but normal triglycerides levels indicate that this PCSK9 variant can also lead to bona fide FH. Grants: ISCIII: DTS16/00196; Generalitat de Catalunya and FEDER: SLT002/16/00174, 2015 FEDER/S-21, SLT002/16/00306; Fundación Isabel Gemio; Torró Solidari: RAC1/Torrons Vicens; 2020BR-IRSJD-CdTorres. Hiener: None. SPS patients show a broad phenotypic spectrum regarding polyp burden and age of onset and might therefore belong to different entities. Hernández 1, Jana Soenksen2,3, Paul Newcombe1, Manjinder Sandhu4, Inês Barroso2, Chris Wallace1,5, Jennifer Asimit1 1MRC Biostatistics Unit, University of Cambridge, Cambridge, United Kingdom, 2Exeter Centre of Excellence for Diabetes Research (EXCEED), University of Exeter Medical School, Exeter, United Kingdom, 3School of Life Sciences, University of Glasgow, Glasgow, United Kingdom, 4Dept of Epidemiology & Biostatistics, School of Public Health, Imperial College London, London, United Kingdom, 5Cambridge Institute of Therapeutic Immunology & Infectious Disease (CITIID), University of Cambridge, Cambridge, United Kingdom. A.A. Tenaiji: None. Gromoll: None. P01.093.A Trisomy 8 mosaicism in the placenta: a Danish cohort study of 37 cases and a literature review Simon H. For the development and clinical application of novel therapeutic modalities in ALS it is essential to stratify the patients based on their genetic background. Introduction: Childhood osteoporosis is often a consequence of a chronic disease or its treatment. Lefkowitz: A. MicroRNAs (miRNAs) have also been shown to play a role in tumour heterogeneity and CMS-specific biology. Being able to share genetic information with children or relatives (82%), to prevent the birth of a child affected with a hereditary condition (81%) and to know the risk of conceiving a child with a hereditary condition (80%) were the main reasons to accept ECS that were selected by the majority of women. Carrasquilla 1, Mario García-Ureña1, Tove Fall2, Thorkild I. Pranckevičienė: None. Borisov: None. Nevertheless, we find novel genome-wide associations with pregnancy-related traits for the FBLN7, STK32B, and ACTR3B genes, and replicate the effects of the KAZN and TLE1 genes, with the latter being the only gene identified across all data resources. Jędrzejowska: None. The proband suffered a chromosomal unbalance with a partial trisomic component 13q31.1-q34 and a monosomic component 3p26.3 from paternal origin. Using trio-based high-throughput whole locus sequencing (WLS) for second disease alleles, we identified a founder deep intronic mutation (NM_020366.3:c.1468-128T>G) in 3/6 families. Leu232Pro, and p. Doco Fenzy: None. Pedigree was uninformative. Correlation between the degree of retinal pigment epithelium (RPE) atrophy (represented by the area of decreased autofluorescence on fundus imaging) and loss of photoreceptors (represented by outer nuclear layer (ONL) thickness on optical coherence tomography (OCT) and pattern electroretinography (PERG) amplitudes) was compared between groups. Materials and Methods: A clinical investigation was undertaken in 16 kindreds containing two or more cases of NMTC. Newman1,2, Woolf S. This can lead to a feeling of isolaton, which requires special medical follow-up procedures accompanied by regular updating of knowledge. Introduction: Since the approval of PARP inhibitors for the treatment of high-grade serous ovarian cancer that BRCA1 and BRCA2 genetic testing have therapeutic implications (germline and somatic variants) in addition to cancer risk assessment and should be offered to these patients at diagnosis irrespective of family history. Piltonen: None. Aneuploidies were called after only 30 minutes of sequencing, while 30 hours were needed to call CNVs A), not present in the databases of human variation, predicted damaging by "in silico" tools, affecting conserved amino acid residue and described previously in one other patient with intellectual disability of different ethnic origin. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Modest; UCL. Material and methods: A multicentric, Italian WES data sharing has been carried out with the aim of providing a complete clinical and neurocognitive picture of patients with a similar phenotypic characteristic (a diagnosis of POGZ-related disorder), and negative to SNPs/CGH molecular karyotyping. We report the first adult patient with NADSYN1 associated congenital NAD deficiency disorder and thus greatly expand the phenotypic spectrum. More than 90% of ART-BWSp patients reported so far carry Imprinting Center 2 Loss-of-Methylations (IC2-LoM), versus ≈50% of naturally conceived BWSp patients. P15.037.A Personal Automation for Whole Genome Sequencing: Evaluating Digital Microfluidics Across Two Different PCR-free Protocols Eugenia Carvajal 1, Adam Barner1, Julia Yoo1, Preetham Hosur1, Michely Ternadi1, Tom Howd2, Tim Desmet2, Fay Christodoulou1, Mais Jebrail1, Severine Margeridon1 1Miroculus Inc, San Francisco, CA, USA, 2Broad Institute Genomics Platform, Cambridge, MA, USA. In contrast, cases show higher SNP scores compared to controls (p = 0.0045). Čajbiková: None. Antonaros: None. Funding: This project was supported Bezmialem Vakif University, Scientific Research Committee(No:20200917) O.F. Duzenli: None. P09.052.A Rare pathogenic variants in genes of glutamatergic neurotransmission pathway segregate with schizophrenia in Pakistani familiesAmbrin Fatima1,2,3, Uzma Abdullah 4,3,5, Muhammad Farooq6,2, Zafar Ali2, Yuan Mang2, Mana M. In conclusion, our study design using exome analysis of patients with a familial form of ovarian cancer identified candidate genes for hereditary predisposition to high-grade serous ovarian cancer. Tempé: None. Interestingly, several sox family members (sox5, 6, 8 and 18) were shown to be significantly deregulated in shox-deficient pectoral fins among other genes including nppa, nppc; cdkn1a, cdkn1ca, cyp26b1, cyp26c1, highlighting the important role of gene family members in shox-related growth disorders. Adrian1,2, Raimondo M. Mechanical testing of 2-month HET and HMZ showed reduced stiffness, yield and fracture load, with markedly increased brittleness. A multigene panel analysis (brain malformations panel, 400 genes) revealed two likely disease-causing variants; a maternal inherited hemizygous missense mutation c.766G>A, p.Gly256Arg in exon 7 and a paternal inherited heterozygous deletion of exon 6 and 7 of the PHGDH gene. Maximino4, Germana Meroni5, Maria Leine Guion-Almeida6, John M. Lauffer: None. AlShamsi: None. Earlier, according to GWAS, this polymorphic variant showed an association with schizophrenia. D.A. Thorsteinsson: None. Our findings identify the first human disease caused by defective function of a member of the SCUBE family, and link SCUBE3 to processes controlling growth, morphogenesis, and bone and teeth development through modulation of BMP signaling. Conclusions: Accurate characterization of CCRs by molecular cytogenetic methods is important because carriers of such rearrangements can display a wide array of phenotypes. di Bernardo: None. In general the treatment is focused on the prevention of hyperammonemia. In keeping with its mission as the core knowledgebase for mouse-human comparative biology, Mouse Genome Informatics (MGI, www.informatics.jax.org) has implemented a Coronavirus Information portal to streamline access to current mechanistic and therapeutic mouse studies of COVID-19. Cantarín Extrémera: None. It is associated with a reduction in brain volume and often developmental/intellectual disabilities. Kretz: None. Currently, the concept of MVP syndromes is defined as " a stable combination of two or more non-induced by each other malformations in different systems". The aim of this study was to investigate the influence of MSCs on triple negative breast cancer (TNBC) cell lines. About half of the affected individuals had behavioral problems, altered muscular tone, hearing loss, and short stature. Conclusion: This result expands the mutational spectrum of the NCSTN gene. Alvarez1, Siulan Vendramini-Pittoli1, Juliana F. The prevalence of somatic dMMR was also measured in a cohort tested negative for a pathogenic germline variant and MLH1-promoter methylation (n = 125). Eccles: None. In this thesis, we present brief clinical features of 17 patients with MPS-PS in Yakutia. The general symptoms include growth retardation, recurrent joint dislocations, scoliosis, developmental delay, intellectual disability, behavioral problems and distinctive facial features. Case report: The proband is a 23-month-old gild referred for growth delay and genu varum. Results: We analyzed the frequencies of genotypes for the FTO gene 23525T>A polymorphism among 11-15 year old boys depending on the stage of puberty. Freidin2, Yakov A. In UMOG (Ophtalmogenetics Multidiciplinary Unit) we have designed and developed a novel and comprehensive screening strategy for all genes and loci responsible for eoHM on next-generation sequencing (NGS) developing a systematic application and automation in the clinical routine. We detected cell clusters enriched in either evolutionarily old or young TE families, supporting the inclusion of TEs at the 5'-end of genes or the autonomous expression of TEs. These results suggest that TEs contribute to the identity of T lymphocytes in response to the exposure to the tumour microenvironment. Bonache: None. Suchecka: None. Bure: None. Pośpiech: None. P13.030.C Psychoemotional stress induces the changes in the content of satellite III (1q12) and telomere repeats in human leukocyte DNASvetlana V. To date, most genetic studies have focused on particular biological candidates. Gene prioritization was then performed considering data from CanVar (data from ~1000 familial/early-onset CRC patients), IntOGen (information on cancer driver genes), GTEx (gene expression), OMIM and Pubmed. Kiani: A. 246 mots G. Introduction: Array Comparative Genomic Hybridization (aCGH) represents molecular cytogenetic approach for genome-wide detection of copy number variants (CNVs) that allows efficient genetic diagnosis of pathological conditions, such as developmental delay and neurological disabilities. Duchenne Muscular Dystrophy (DMD) is a lethal progressive muscle-wasting disease. Wilcots: A. Results: Reanalysis of WES data from case 1 revealed two compound likely pathogenic heterozygous variants in VARS2 gene: c.1258G>A, p.(Ala420Thr) and c.1100C>T, p.(Thr367Ile). J.W. Oketch: None. Heritability in Europeans (UK-Biobank) was 22.3%. (Crippa et al., 2019) ANKRD11 and SETD5 have been identified as chromatin regulators involved in gene expression. Aliaga: None. Introduction: The publication of the UK British Society for Genetic Medicine's (BSGM) consent and confidentiality guidance in July 2019 highlighted the need and desire for separate and updated guidelines in two areas, genetic testing in childhood, and prenatal genetic testing. Cogne: None. Conclusion: Patients with PPARG mutations may develop lipodystrophy due to defective adipocyte differentiation. Fine-mapping of those regions in association study using exome sequencing identified SEMA3A (p-value = 8.5·10-4), PPP1R9A (p-value = 7.2·10-4), PUS7 (p-value = 8.7·10-4), CDHR3 (p-value = 7.2·10-4), HBP1 (p-value = 1.5·10-4) and COG5 (p-value = 1.5·10-4) genes with p-values below significance threshold. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Modest; Novartis, Pfizer. M.A. Mensah: None. Whole exome sequencing analysis of patient's DNA revealed the novel heterozygous nonsense variant c.646C>T, p.(Gln216Ter) in the SMARCA4 gene. These included osteoarthritis, smoking, drinking, attention-deficit hyperactivity disorder, and various metabolites. Haplotype and conditional analyses pointed to disease-contribution by the common variant c.53T>A/p.Ile18Asn. CNVs were called with four different variant callers (ClinCNV, ExomeDepth, Conifer, VarGenius). Likelihood Ratios (LR) were calculated for each histopathological feature, and were aligned to ACMG/AMP strengths. Further investigation of data found in-frame deletion p.91_97del in SLC34A1 gene with global frequency 1,7% in two patients in compound heterozygous state, that previously was described as pathogenic. Khan2, Christian Windpassinger1 1Diagnostic & Research Institute of Human Genetics, Graz, Austria, 2Gomal Centre of Biochemistry and Biotechnology, D. Among them, 21 (3.4%) had two pathogenic variants and 20 additional patients had one pathogenic and one variant of unknown significance (VUS) with a high probability of being reclassified as likely pathogenic in the future, raising the rate to 6.7%. In contrast, polyploidy and mosaicism were more frequent in FISH-analyzed compared to the karyotyped group: 26.2% (105/401) vs 16.9% (306/1814) (p 7.15 Mb), ventricular septal defects and kidney abnormalities were also observed. Porphyromonas gingivalis,Tannerella forsythia, Fusobacterium nucleatum, and Treponema denticola, were able to disseminate from the oral cavity and invade atherosclerotic plaque in humans. Here, we rebuild the ReMM score (Smedley D. Institute of Genetic Diseases, Imagine and Paris Descartes University, Paris, France, 5Centre de Référence des Affections Sensorielles Génétiques, Institut des Neurosciences de Montpellier, CHU-Saint Eloi Montpellier, Montpellier, France, 6Eye Clinic Jules Verne, Nantes, France. Compared to the middle 50% of the population, the upper quartile had 41% increased risk and the lower quartile had a 24% decreased risk. P09.082.C Analysis of the most common nuclear genome encoded mitochondrial gene in Hungarian patients with adult-onset mitochondrial disorders Fruzsina Szabo 1, Zoltan Groszl1, Andras Gezsi2, Anna Suveges1, Idris J Jimoh1, Helga Zeke1, Aniko Gal1, Mária Judit Molnár1 1SOTE, Institute of Genomic Medicine and Rare Disorders, Budapest, Hungary, 2BME, Faculty of Electrical Engineering and Informatics (VIK) Department of Measurement and Information Systems, Budapest, Hungary. P15.046.B Application of a novel instrument-free and microfluidics-free single-cell analysis technology (PIPseq) that is well suited for viral applications in resource constrained laboratoriesJacquelyn Turcinovic1, John Connor1, Aaron May-Zhang2, Ahmad Osman2, Robert Meltzer 2, Sepehr Kiani2, Kristina Fontanez2 1Boston University, Boston, MA, USA, 2Fluent BioSciences, Watertown, MA, USA. Alcaide: None. Clinical exome sequencing was performed on DNA extracted from the sample, using Sophia Genetics' Clinical Exome Solution v2. Suspitsin 1,2, Elizaveta Y. Siegal: A. After thorough yet inconclusive clinical genetic testing to uncover the cause of neurodegenerative symptoms in a father and his daughter, our lab was tasked to do a more in-depth genomic investigation of the family. Consultant/Advisory Board; Modest; Idorsia, Neuron23, Handl Therapeutics, Lysosomal Therapeutics Inc, Deerfield, Lighthouse, Prevail Therapeutics, Ono Therapeutics, Denali, Inception Science. Data gaps were filled using information from national specialty organisations. Introduction: Mitochondrial diseases are a group of heterogeneous inherited metabolic diseases, caused by a dysfunction of the mitochondrial respiratory chain. The genomic region flanking the CRISPR target site was amplified and sequenced. Results: We tested the software on samples with contamination added in-silico, and determined that the software correctly identifies the source and quantity of contamination, even when multiple contaminants are used. The structural variant detected two novel heterozygous deletions in the 5' Untranslated region of GNAS gene for each sibling, 466 bp and 1439 bp respectively. Similarity assessment of these CNV profiles along with examining single nucleotide variants as well, enable the detection of cell lines that are the most accurate representations of the disease. Jolly: None. Those with two missense variants had a mild to severe hearing loss, which could be of secondary onset. Serbezov: None. P24.046.A Polygenic Risk Score Estimation in North-Western Russian Population Valeriia Rezapova 1,2, Nikita Kolosov1,2, Oxana Rotar1, Olga Freylikhman1, Alexander Loboda1,2, Olesya Melnik1, Alexey Sergushichev2, Andreas Gnirke3, Christine Stevens3, Alexander Meissner4, Anna Kostareva1, Alexandra Konradi1, Mark J. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Modest; Fluent BioSciences. P09.108.A De novo variants in the lysinedemethylase PHF2 are associated with developmental delay, autistic behavior, and facial dysmorphism Alexej Knaus 1, Miriam Wojcik2, Miriam Viktor3, Katheryn Grand4, Pedro A. In the process of our optical genome mapping verification study, 7 cases with an apparently balanced translocation were examined to gain deeper insight into the translocation breakpoints. Patients: We retrospectively evaluated the results from WES-based gene panels in CHD patients in the Netherlands at the University Medical Center Groningen (UMCG) and the University Medical Center Utrecht (UMCU). cDNA analysis of the patient's blood showed that the MLH1 variant causes exons 9 and 10 skipping, which supported our assessment of the variant as likely pathogenic according to the ACMG guidelines. Study was supported by a grant from the Ministry Education and Science, Republic of Kazakhstan (AP09563474). This variant creates frameshift with premature termination codon (p.Thr589ProfsTer66) which is known mechanism of MODY. Fauria: None. Patient 3 has a history of autism spectrum disorder, migraines, chronic fatigue, muscle weakness, and gastroesophageal reflux. Zemánková: None. As a control, copy number was determined (417 for AMY2 and 472 for AMY1) from DNA samples of healthy people. The SCA1 mutation in Yakutia are distributed over the following geographic foci - Northern (Indigirka River), Central (Lena-Aldan interfluve) and Southwestern (Vilyui and Lena rivers). Conclusions: In our case, the diagnosis was delayed beyond the second life decade, this illustrates the difficulty of correctly diagnosing patients with Myhre syndrome. Then, we integrated DNA-seq and RNA-seq variants to detect allelic imbalances. Hotspot mutations in 22 oncogenes (KRAS, EGFR, BRAF, PIK3CA, AKT1, ERBB2, PTEN, NRAS, STK11, MAP2K1, ALK, DDR2, CTNNB1, MET, TP53, SMAD4, FBX7, FGFR3, NOTCH1, ERBB4, EGFR1, FGFR2) were detected using NGS (Ion Torrent™ PGM) Ion AmpliSeq colon and lung cancer research panel (ThermoFisher). Carrio-Cordo: None. Zinchenko1,3 1Research Centre for Medical Genetics, Moscow, Russian Federation, 2Republican Children's Clinical Hospital, North Ossetia-Alania, Vladikavkaz, Russian Federation, 3N.A. Semashko National Research Institute of Public Health, Moscow, Russian Federation. Method-Case Report: A pregnant woman was referred at 22 weeks to our tertiary care center for sporadic arthrogryposis, 'unusual thin left leg', 'clinodactyly', normal growth parameters in a female fetus. Methods: Patients from the institute's biobank (NEPSYBANK) were selected for the study (N = 116). Xue: A. Broly: None. 57 out of the total of 132 suspected healthy carriers (43.2%) were positive for CFTR mutations in a heterozygous status. Pirastu: None. P10.040.D Expanding disease spectrum of muscular dystrophy Marwan Nashabat, Şahin Avcı, Esra Börklü-Yücel, Hilal Pırıl Saraçoğlu, Piraye Oflazer, Nathalie Escande-Beillard, Hülya Kayserili Koç University, Istanbul, Turkey. Attard: None. Borghese: None. Bruque2, Sebastián Menazzi3, Liliana Francipane3, Vanesa Lotersztein4, Ana B. P15.006.B Automation of NGS library preparation for cancer panels Kristina Lu, Zachary Smith Beckman Coulter Life Sciences, Indianapolis, IN, USA. Conclusions: We have developed a large-scale functional approach to measure the impact of all missense variants in the RAD51C gene using PARP inhibitors sensitivity as a readout. In silico study demonstrated favourable docking into the binding sites of BCL2 and EGFR proteins. Illarionov 1,2,3, Olga V. We benchmarked established and deep learning splice prediction tools on gold standard sets of variants in the ABCA4 and MYBPC3 genes associated with Stargardt disease and cardiomyopathy, respectively, with functional assessment splice assays. Model features capture all characteristics of a variant combination and its association with patient's phenotypes at variant, gene and gene-pair level. The highly conserved 2-enzyme NAD(P)+ repair pathway eliminates toxic NAD(P)HX metabolites that accumulate in inflammatory stress. Samples were taken before treatment. Tartaglia: E. Prendiville: None. Guchelaar: None. One third of the diagnosis led to TOP. P22.015.B An international plan for education, awareness, commemoration and celebration of the July 2022 Bicentennial of Gregor Mendel's Birth in Brno Czechia Milan Macek Jr. 1, Maurizio Genuardi2, John J. Flicek: None. Conclusions: When using NGS sequencing, clinical symptoms and positive biochemical markers, greatly improves the percentage of genetic diagnosis in patients with suspected IMD. Houdayer: None. The gene-based scores are derived from allele frequency and functional annotations of variants of coding-region. This variant is frequently reported in HAE-nC1-INH patients and is considered pathogenic under ACMG classification guidelines. Segnali: None. Background: In September 2017, Sanford health launched a preemptive genomic screening program by inviting a small cohort of patients already enrolled in our Biobank to participate without payment, resulting in a 37% enrollment rate. This pipeline will benefit from having both WGS data and gold-standard PCR genotypes of multiple REs. Despite being highly heritable, pathogenic variants are only identified in approximately 15% of ALS cases. Targeted resequencing found association of rare exonic variants in CNTN5 with worse functional outcome (p A in the proband. Pituello: None. Heise: None. However, the complete phenotypical impact of these germline mutations remains unknown. Matveeva State Research Center of Virology and Biotechnology "Vector", Rospotrebnadzor, World-Class Genomic Research Center for Biological Safety and Technological Independence, Federal Scientific and Technical Program on the Development of Genetic Technologies, Koltsovo, Novosibirsk Oblast, Russian Federation. Additionally, information on referral criteria for familial cardiovascular disease for the general practitioner to act upon a potential risk was recommended. Pelo: None. Grants: EVA (KP111513), MUMC+; Horizon 2020 innovation (ERIN) (EU952516), European Commission; RFBR (20-315-90111) R. pre intervention in the intervention compared to the placebo control group. AlSayed: D. Materials and methods: Fold changes in expression levels of CXCL12 and ETV5 were determined by quantitative PCR in non-obstructive azoospermia (NOA) (n = 10) patients with SCOS and obstructive azoospermia (OA) (n = 2) as control cases. She had brachycephaly with flat occiput, wide forehead, strabismus, monolateral ptosis, epicanthic folds, low-set, prominent, posteriorly rotated ears, long and smooth philtrum, thin lips, high-arched palate, microretrognathia, short 4th and 5th metacarpal bones, lumbar hyperlordosis. Buson: None. However, this is the first time to our knowledge that the allele and genotype frequencies of rs533984 have been found to differ between old and young cohorts. Despite their relevance in disease-oriented research, sequencing FFPE and cfDNA samples remain challenging due to their low DNA quality and quantity. Previous studies in C. Machado: None. O'Mahony: A. Germline missense mutations in the HRAS gene cause Costello syndrome (CS), a rare developmental disorder characterized by a typical facial gestalt, postnatal growth deficiency, intellectual disability, predisposition to malignancies as well as skeletal, cardiac and dermatological abnormalities. Materials and Methods: Five families including 10 subjects with FML and two healthy family members were recruited. In the 54 cases having a molecular diagnosis, 57.4% (n = 31) were diagnosed with red cell membrane protein defects and 42.6% (n = 23) with enzyme deficiencies. Case report: Here we describe a familial case of CF with three children: 11 yo and 8 yo siblings with classical CF phenotype had positive NBS and elevated sweat chloride test results. Additionally, we started collaboration with Unique and information on various RDs will now be available in Georgian language as well. Genes uniquely associated with a single trait of the syndrome were often well known from physiology and/or monogenic disease. The level of significance of the genetic association with the pathological phenotype was analyzed through PhenoScannerto investigate if any SNPs show eQTL associations of significant expression and consequently quantify the regulatory effect of the risk variants. Materials & Methods: Eight patients were enrolled in the study aged 28-51. Acknowledgements: Work supported by the Instituto de Salud Carlos III (PI17/01067), co-financed by Fondo Europeo de Desarrollo Regional (FEDER) "una manera de hacer Europa" and AGAUR (2017 SGR1134). Clinical and survival data were collected for each patient. Materials and Methods: 321 newborns from a cohort of pregnant women from Qingdao, China, underwent high-depth GS with the approval of the ethics committee. Results were discussed with the physicians of the reference center for Skeletal Dysplasias. Although TTR is the only known RBP transporter that facilitates the transport of retinol, there are two other T4 transporter proteins: albumin and thyroxine binding globulin. To generate additional evidence to better interpret the effects of missense VUS, we developed a gene-specific functional modeling platform (FMP) evaluating DNA sequence conservation, biophysical, structural, cellular, and spatial relationships within an observed missense change setting. Trimouille: None. Facultad de Ciencias Exactas y Naturales,Universidad de Buenos Aires, CABA, Argentina, 6Departamento de Neonatología, Hospital Gandulfo, El Calafate, Santa Cruz, Argentina, 7División de Genética, Hospital de Clínicas "José de San Martín", Universidad de Buenos Aires, CABA, Argentina, 8Fundación para la Prevención de la Muerte Súbita, CABA, Argentina. Result: Internal gene-matching using a local exome database allowed the identification of a homozygous splice-site variant in MADD (c.2816+1G>A) on a common haplotype in all four families, indicating a founder variant. Ophtalmology Department, San Giovanni di Dio e Ruggi d'Aragona University Hospital, Salerno, Italy, 44. Aydos: None. Zarubina: None. Yet, how the active X in both males and females is protected from being silenced by its own XIST locus is not well understood in any mammal. The frequency of psychiatric, neurologic and skeletal findings may increase with follow-up data of current patients. Nance-Horan syndrome is an X-linked disorder characterized by congenital cataracts, dental anomalies, and other features. Horn: B. However, for rare missense variants the clinical significance is unknown. Up to now, 5 pathogenic variants were reported to be cause of CACNA1B associated NEDSNEH, and we present this novel variant detected in our case as the 6th variant. Methods: Our transdiagnostic sample (n = 1042) of individuals diagnosed with MDD, BD, SCZ, or SZA was recruited from the German FOR2107 cohort. Anna University Hospital of Ferrara, Ferrara, Italy, 3Maria Cecilia Hospital, GVM Care & Research, Cotignola, Italy. Introduction: Metaphyseal dysplasia, Spahr type (MDST, MIM#250400) is an ultra-rare metaphyseal dysplasia likely often mistaken as rickets. It would be useful to perform molecular analysis for establishing the affected gene. In addition to the neuromuscular involvement, DMD often presents with cognitive and neuro-behavioural co-morbidities, for which the pathogenesis and genotype-phenotype relationship are partially understood. Martinková: None. A custom pipeline for variant prioritization was carried out to obtain candidate variants and Copy Number Variants (CNVs). Our results suggest that customized panels and clinical exome would be the first-tier approach in the naïve cases, whereas whole-exome sequencing would be in the re-studied and reanalysed. Moreover, previously unpublished genotypes, communicated by 7 reference laboratories worldwide were included in the analysis. Lorenzo-Salazar4, Rafaela González-Montelongo4, Almudena Corrales1,5, M Isabel García-Laorden3,5, Miryam Prieto-González6, Aurelio Rodríguez-Pérez7,8, Demetrio Carriedo9, Jesús Blanco5,10, Alfonso Ambrós11, Elena González-Higueras12, Elena Espinosa13, Arturo Muriel10, David Domínguez13, Abelardo García-de-Lorenzo14, José M. F3 had pedigree suggestive for X-linked inheritance and WES, widely used technique, was utilized. Discover DysplasiasTM sponsored testing program offers a focused SD gene panel for US and Canadian patients, with the goal of helping facilitate timely diagnoses. All tested variant callers performed worse in regions with higher fraction of multimapping reads, and mappability and GC content were the greatest sequence-based confounders for all variant callers. We reported similar SNP-heritability than previous studies and highlighted a significant positive correlation between HGS and bone density and fracture risk PRS. For detailed comparison, we reviewed all published characterizations of the NONO-associated disorder. Diagnosis is often delayed due to a normal result in the lymphocytes. Bioinformatic analysis was performed using algorithms developed by our bioinformatic unit. Parental studies indicated this variant to be maternally inherited, so it is considered unlikely to be disease causing. This project is co-financed by the Connecting Europe Facility of the European Union, under the Action Number 2018-FR-IA-0184. Conclusions: Our results suggest that the SCN4A variant c.794C>T may explain the cause of muscular weakness in our proband and further broaden the spectrum of AR inheritance for SCN4A. Dale: None. 2018). Zoli: None. Probands showed increased number of missense mutations in MT-ATP6 and MT-ATP8 and reduced mtDNA content. Heterozygous pathogenic mutations in CDK13 are inherited in an autosomal dominant manner characterized by congenital heart defects, dysmorphic facial features, and intellectual developmental disorder2. Aktuna: None. Exon deletions and long deletions are reported for BRCA1 and BRCA2. van Swieten1, Jeroen G. Kruuse: None. P11.101.C Low risk of embryonal cancer in PIK3CA-Related Overgrowth Spectrum: impact on screening recommendations Laurence Faivre 1,2, Jean-Charles Crépin1,3,4, Manon Réda5, Sophie Nambot5, Virginie Carmignac1,4, Caroline Abadie6, Audrey Putoux7, Juliette Mazereeuw-Hautier8, Aude Maza8, Maxime Luu9, Yannis Duffourd1, Christophe Philippe1, Christel Thauvin-Robinet1, Martin Chevarin1, Claire Abasq-Thomas10, Jeanne Amiel11, Stéphanie Arpin12, Geneviève Baujat13, Didier Bessis14, Emmanuelle Bourrat15, Odile Boute16, Anne-Claire Bursztejn17, Nicolas Chassaing18, Christine Coubes19, Patrick Edery7, Salima El Chehadeh20, Alice Goldenberg21, Smail Hadj-Rabia22, Damien Haye23, Bertrand Isidor24, Marie-Line Jacquemont25, Didier Lacombe26, Bruno Leheup27, Ludovic Martin28, Anabel Maruani29, Fanny Morice-Picard26, Florence Petit16, Alice Phan30, Lucille Pinson19, Eve Puzenat31, Massimiliano Rossi7, Renaud Touraine32, Clémence Vanlerberghe16, Marie Vincent24, Catherine Vincent-Delorme16, Sandra Whalen33, Marjolaine Willems19, Tristan Mirault34, Paul Kuentz1,35, Pierre Vabres1,3,4,2 1Equipe INSERM UMR1231, Génétique des Anomalies du Développement, Université Bourgogne Franche-Comté, Dijon, France, 2Fédération Hospitalo-Universitaire Médecine Translationnelle et Anomalies du Développement, CHU Dijon Bourgogne, Dijon, France, 3Service de Dermatologie, CHU Dijon Bourgogne, Dijon, France, 4Centre de référence Maladies Rares Génétiques à Expression Cutanée (MAGEC), CHU Dijon, Dijon, France, 5Service de génétique, CHU Dijon Bourgogne, Dijon, France, 6Département d'Oncologie Médicale, Saint-Herblain, France, 7Département de Génétique, Hospices Civils de Lyon, Lyon, France, 8Service de Dermatologie, CHU Toulouse, Toulouse, France, 9Centre d'Investigation Clinique – module plurithématique, CHU Dijon Bourgogne, Dijon, France, 10Département de Pédiatrie et Génétique Médicale, CHU Brest Morvan, Brest, France, 11Service de Génétique Médicale, Hôpital Necker Enfants Malades, Paris, France, 12Service de Génétique Clinique, CHRU de Tours, Tours, France, 13Service de Génétique Médicale, Hôpital Necker-Enfants Malades, Paris, France, 14Département de Dermatologie, CHRU de Montpellier, Montpellier, France, 15Service de dermatologie, CHU St-Louis Lariboisière, Paris, France, 16Service de Génétique Clinique, CHU Lille, Lille, France, 17Service de Dermatologie, CHU de Nancy, Nancy, France, 18Service de Génétique Médicale, CHU Toulouse, Toulouse, France, 19Département de Génétique Médicale, Maladies rares et Médecine Personnalisée, CHRU de Montpellier, Montpellier, France, 20Service de Génétique Médicale, CHU de Strasbourg, Strasbourg, France, 21Service de Génétique, CHU de Rouen et Centre Normand de Génomique Médicale et Médecine Personnalisée, Rouen, France, 22Service de Dermatologie et Centre de Référence des Maladies Rares Génétiques à Expression Cutanée (MAGEC), Université Paris Descartes-Sorbonne Paris Cité, Institut Imagine, Hôpital Universitaire Necker-Enfants Malades, Paris, France, 23Service de Pédiatrie, CHU de Tours, Tours, France, 24Service de Génétique Médicale, CHU de Nantes, Nantes, France, 25Unité de Génétique Médicale, CHU de la Réunion, Saint Pierre, France, 26Service de Génétique Médicale, CHU de Bordeaux, Bordeaux, France, 27Service de Génétique Clinique, CHU de Nancy, Nancy, France, 28Service de Dermatologie, CHU d'Angers, Angers, France, 29Service de Dermatologie, Unité de Dermatologie Pédiatrique, Tours, France, 30Service de Dermatologie, CHU de Lyon, Lyon, France, 31Service de Dermatologie, CHU Besançon, Besançon, France, 32Service de Génétique Clinique, CHU de Saint-Etienne, Saint-Etienne, France, 33Unité Fonctionnelle de Génétique Clinique, Hôpital Armand-Trousseau, Paris, France, 34Centre de référence des maladies vasculaires rares, Centre Européen Georges Pompidou, Paris, France, 35Génétique Biologique Histologie, CHRU de Besançon, Besançon, France. The goal of this study is to find modules of genes related to CSC. Results: Ten cases of mosaicism for whole chromosome aneuploidy(mWC) and five cases with mosaicism for (sub)chromosomal copy number variations(mCNVs) were included. 36 reports were returned to the GP. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. E.N. Tolmacheva: None. Aro: A. McGaughey: None. G.H. Mochida: None. Many other drugs are inefficiently metabolized in these patients, including antidepressants (Doxepin, Trimipramine, Imipramine), and selective estrogen receptor modulator Tamoxifen, used for treatment and prevention of breast cancer. Szegedi: None. Through assessing this data, we will utilise mixed methods to determine the challenges experienced and how services have adapted and developed resilience to provide the best possible service to patients in the landscape of COVID-19 and beyond. K.V. Vagaitseva: None. Additionally, five naevi removed before the MM were analyzed for genetic alterations. Rehker: None. There is growing evidence for the importance of 3'UTR dependent regulatory processes, particularly in large polarised cells such as neurons. MLH1 and PMS2 proteins form a functional dimer MutLα, the stability of which can be tested using the yeast two-hybrid system (Y2H). Dominguez Rodriguez: None. P01.009.A Genetic analysis of azoospermic men by an integrated NGS panel Monika Logara Klarić 1, Lovro Trgovec-Greif1, Lucija Žunić2, Filip Rokić1, Ana Vičić3, Tihana Marić4, Ana Merkler5, Ana Katušić Bojanac4, Robert Beluzić1, Feodora Stipoljev3, Oliver Vugrek1, Maja Barbalić2,6 1Ruđer Boškovic Institut, Zagreb, Croatia, 2Genom Ltd., Zagreb, Croatia, 3Department of Obstetrics and Gynecology, Clinical Hospital "Sveti Duh", Zagreb, Croatia, 4Department of Medical Biology, University of Zagreb School of Medicine, Zagreb, Croatia, 5Department of Laboratory Diagnostics, University Hospital Centre Zagreb, Zagreb, Croatia, 6Department of Medical Biology, School of Medicine, University of Split, Split, Croatia. Perez: None. Although ferroptosis has recently been studied in epilepsy, the genetics underlying this process remain unclear. Ben-Haim: None. Since 2005, clinical symptoms associated with mucopolysaccharidosis-plus have been recorded in Yakut patients; previously undescribed storage disease with an autosomal-recessive type of inheritance was suspected [Gurinova E.E. 2014]. Multiple tumors of the left kidney and lung cysts were observed upon clinical and laboratory testing. Clinical suspicion of mosaic monosomy 13 was raised following a case report in the literature, and prompted analysis of a skin biopsy. In VWF gene analysis, 21 different variants associated with the VWD type 3 were identified and nine of them were frameshift, five missense, five nonsense and two splice site mutation. Results: A total of 205 patients were analyzed, clinical data were available in 64% of cases (132/205) and the genetic diagnosis was reached in 34% of the patients (45/132). The survey assessed four broad areas: awareness of national and UK-wide genomics initiatives and attitudes to genomics; current professional practice and genomics competency; genomics and the workplace (including support from colleagues and work environment); and influencing factors. Koval: None. Proskorovski-Ohayon: None. Two of the latter encoded the glycosyltransferase enzymes FUT6 and FUT8. Methods: We combined GWAS on 36,173 individuals from the pan-European EPIC study, including 10,855 T2D cases, 4,126 postmenopausal breast, 2,111 colorectal, 473 pancreatic and 419 prostate cancer cases. Vieira: None. Methods: An asymptomatic 4-year-old boy without family history of neuromuscular disorders was referred to us due to incidental findings of elevated CK (2160-3335 U/L). Clinical and molecular characterization of further patients with 13q deletions might contribute to its better genotype-phenotype correlation and understanding of pathogenesis. We revealed DEGs of nucleic acids and protein metabolism (Tlr7, Cd48, Stk17b, Eif2ak2, Fli1) for Selank; DEGs linked to lipid binding (Apol3, Apol9a), and the regulation of ion channels (Grin2a, Arc, Slc6a13) for Semax; and DEGs associated with the functioning of proteasomes (Psma8, Psmb11, Psmb8, Psmb9), and DNA replication (Mcm3) for ACTH(6–9)PGP action. Kammoun: None. severe monogenic actionable mutations), and evaluation criteria (health expenditure vs. P04.062.C Analysis of single-cell based expression variability between candidate genes for syndromic and non-syndromic forms of orofacial clefting Anna Siewert 1, Julia Welzenbach1, Benedikt Reiz2, Elisabeth Mangold1, Henning Dickten2, Kerstin U. Introduction: DDX3X related neurodevelopmental disorder (DDX3X-NDD) is a very rare entity, with less than 200 cases described in literature, caused by mutation in DDX3X gene (Xp11.4). A.T. Vulto-van Silfhout: None. Ciocan: None. R.A. Maksyutov: None. Carrascosa: None. Cases: We report two patients with a syndromic neurodevelopmental disorder whose clinical exome revealed novel variants in WAC gene. B.W. van Bon: None. Kronenberg: D. The discrepancy between the phenotypes, coupled with comparable SHANK2 levels in the deletion patient and controls, suggests that the altered phenotype might be caused by genetic factors independent of SHANK2 expression. Dasgupta: A. Introduction: Oxidative stress-related proteins NFE2L2, HMOX1 and TXNRD2 play a role in breast cancer (BC) pathogenesis. We describe the development of in-vitro and ex-vivo tools for the functional characterization of potentially spliceogenic variants and their impact on the canonical PAX6 splicing. Final diagnoses included retinitis pigmentosa, Usher syndrome, cone-rod dystrophy and Leber congenital amaurosis and two rare cases of Knobloch and Oliver-McFarlane syndromes due to mutations in the COL18A1 and PNPLA6 genes, respectively. It suggests their increasing role in rare diseases and the great value of taking them into consideration within a laboratory diagnostic routine. Conclusions: GSPT2 missense variants seem to cause a severe x-linked epileptic encephalopathy, whereas larger deletions including GSPT2 cause a milder intellectual disability. Bouman: None. Our study showed that routine shallow sequencing designed for aneuploidy detection in cfDNA may be sufficient for higher resolution NIPT, if specialized copy number software is used and if sufficient fetal fraction is present. While co-injection of MO together with human PLXNA1 mRNA resulted in a rescue of phenotype, the impact of human alleles in PLXNA1 is being tested in this model. Alhashem: None. We evidenced that missense ITSN1 variants (3/12 variants) without splicing defect predicted are spatially clustered in C-terminal in an important regional missense constraint. Herein, we report on two unrelated patients with a novo 16p13.11p11.2 triplication detected by CMA sharing a similar phenotype including hypotonia, severe neuro-developmental delay with profound speech impairment and hyperkinetic behavior, chronic otitis media and distinctive facial features. The main morphology was adenocarcinoma - 36 (74%). Rodenburg5, Marieke J. M.S. Uppal: None. Introduction: Genetic abnormalities such as hyperdiploidy and hypodiploidy influence outcome during therapy of childhood B-cell precursor acute lymphoblastic leukemia. We aim to expand the phenotype studying a cohort of patients, describing their expected and unexpected clinical features. It remains to be determined if this is the case for other rearrangements of the LDLR gene in the CR. We recommend initiating WES as early as possible due to the impact on management and family counseling. Potential additional diagnoses are currently being investigated. P12.160.D Investigation of Wnt signaling pathway components in VPA induced PANC 1 cellsYeliz Ekici1,2, Abdullah Yilmaz3, Umut Kucuksezer3, Sema Bilgic Gazioglu3, Zeynep Dogusan Yamalioglu4,5, Ali Osman Gurol3,6, Thomas Linn7, Feyza N. Five variants including rs1800796 had Fis negative, indicating an excess of heterozygotes. In Sertoli cells, aberrant activation of canonical WNT signaling keeps them immature, which may interrupt male fertility via progressive degeneration of seminiferous tubules. Jiménez Rodríguez: None. Mackenzie: D. Weisburd: None. We studied various hematological and epigenetic signatures of these two groups. Artomov: None. Styka: None. The hub genes including FOXK2, EFNA5, XPC, VGLL4, ELP1, MKKS, LIN7B, STS, ZNF23 and ZNF71, which may be potential biomarkers or therapeutic targets for HGSOC, have been identified. Mice from each group were treated with chaperones or vehicle for 2, 6 or 12 months. Families CYP 1, 2, and 3 are responsible for the biotransformation of most xenobiotics, including 70-80% of all drugs in clinical use. Alastalo2 1Blueprint Genetics, a Quest Diagnostics Company, Espoo, Finland, 2Blueprint Genetics Inc, a Quest Diagnostics Company, Seattle, WA, USA. Material and Methods: We included 212 CL/P cases eligible for WES-based gene panel testing between 2015 and 2020 as part of routine care. Large copy number variations (CNVs) represent a significant fraction of genomic alteration in human disease. Whenever necessary, the Human Phenotype Ontology terms were manually inspected according to the declared phenotypes. Abdelhedi: None. Fonti: None. José D. R.B. Hufnagel: None. Al-Ali: A. Results: Among the RA patients, 64 (55 women, 9 men) had low BMD comprising of 57 patients with osteoporosis and 7 with osteopenia. Results: We created a system of 8 plasmids containing all 10 coding exons of the PAX6 gene. All articles that included one or more genetically proven RASopathy and described the lymphatic phenotype were included. We also reviewed published and grey literature, and conducted interviews of key individuals using a semi-structured process to understand differing perspectives on the utility of PGS. Introduction: The epidemiological data represent a significantly increased risk of various cancer forms in patients with diabetes. Conclusions: Integrative transcriptomic analysis of in vitro 7q11.23-CNVs cellular models reveals genes and pathways altered during early neuronal development in these genomic disorders, which could lead to novel potential therapeutic targets. Recently, we reported that methylation levels of the mitochondrial displacement loop (D-loop) region, which regulate mitochondrial DNA (mtDNA) replication, are impaired in peripheral blood cells of late-onset Alzheimer's disease and amyotrophic lateral sclerosis patients. Changes in alternative splicing patterns can lead to partial or total loss of protein functional domains, thereby affecting tumorigenesis, progress and prognosis. P06.057.B Circulating DNA methylation biomarkers for type 2 diabetes diagnosis from saliva Manuela Hofner 1, Ulrike Kegler1, Klemens Vierlinger1, Anja Buhmann1, Michael Leutner2, Walter Pulverer1, Alexandra Kautzky-Willer2, Christa Noehammer1 1AIT Austrian Institute of Technology GmbH, Molecular Diagnostics Unit, Vienna, Austria, 2Medical University of Vienna, Clinical Division of Endocrinology and Metabolism, Vienna, Austria. Prediction websites considered this mutation as a pathogenic variant. Four loci showed association with INV.S: HLA DRB1*15:01 (P = 0.014), rs11751659 (P = 0.02), rs9271366 (P = 0.003), SNP_DRB1_32660116_A (P = 0.036). Procopiuc: None. Francannet: None. Cesaretti: None. Greater awareness of adult specialties towards this group of diseases is necessary. Before a cervical cerclage we performed a routine cytogenetics study. F.M. Torun: None. Groothuismink1, Hanneke I. Carré: None. These results may have important implications in identifying the biological origins of spinal muscular atrophy disorder. tropicalis whole embryo. It will be enriched with documents and courses already available in our network. Mikštienė: None. Two of these patients had a disruption of regulatory elements: one in MEF2C TAD and the other in SOX9. PHGDH is characterized by congenital microcephaly, psychomotor retardation and seizures whereas it has been assumed that NLS1 could be caused by more severe PHGDH-mutations with main clinical features of intrauterine growth retardation (IUGR), microcephaly, cutaneous and craniofacial abnormalities. Molecular modelling was performed to evaluate putative functional consequence of the NIPA1 protein. However, the termination rate in cases with sex chromosome triploidy is unduly high. M.C. Ergoren: None. A duplication of chromosome 7 harboring MET p.(Leu1130Ser) was found in array CGH. D.C. de Souza: None. Cellular reprogramming is a good approach to overcome the experimental limitations to study neurodevelopmental disorders in humans. Baldassarre: None. It is characterized by a metabolic reprogramming suggesting a major role of mitochondria in tumor development. However, the heterozygous GA genotype of the Keap1 rs11545829 polymorphism was associated with increased risk of developing autoimmune thyroiditis. Bolognini: None. Our study enables us to predict and validate the pathogenicity of newly identified variants. This study aims to identify variants associated with PCa and correlate them with clinical data in younger and older patients.Patients and Methods: A NGS target enrichment panel (CELEMICS) was used to analyze 4 genes (SRD5A1, SRD5A2, NR3C1, AR) associated with PCa. We included 8 paraffin-embedded samples derived from: 5 older patients diagnosed with castration resistant PCa and de novo metastatic PCa, and 3 younger patients with low-grade PCa. All samples were sequenced on the Illumina Miseq and the variants were analyzed using the VariantStudio Software. P10.054.B Role of SMN in the nucleolar reorganization after DNA repair Shaqraa musawi 1,2, Lise-Marie Donnio1, Giuseppina Giglia Mari1 1Institut NeuroMyoGène, LYON, France, 2Department of medical laboratory technology, Jazan, Saudi Arabia. Sorosina: None. Variant calling was addressed for different genomic features, separating small indels (SI), Structural Variants (SV) and Copy Number Variants (CNV). N.M. van Schoor: None. Genetic analyses using RASopathy genetic panel comprising 18 genes (PTPN11, BRAF, CBL, HRAS, KAT6B, KRAS, LZTR1, MAP2K1, MAP2K2, NF1, NRAS, RAF1, RASA2, RIT1, SHOC2, SOS1, SOS2, SPRED1) or WES were applied. In total, 59 publications could be included. The mutations cd8[-AA] and IVS2.1[G>A] were not identified in former studies. Martínez-Atienza: None. Congenital imprinting disorders (CID) such as Beckwith-Wiedemann Syndrome (BWS) and Silver-Russell Syndrome (SRS) may be associated with multi-locus imprinting disturbances (MLIDs). Jaschke: None. Results: The patients were two boys aged 9 and 6 years old respectively. Introduction: Acute myeloid leukemia(AML) is a heterogeneous group of disorders, seen predominantly in adults. P24.008.C Coeliac disease phenotypic variation unraveled by disease-susceptibility loci in a deeply phenotyped Finnish cohort Juliana Xavier de Miranda Cerqueira 1, Päivi Saavalainen2, Kalle Kurppa3, Pilvi Laurikka1, Heini Huhtala4, Matti Nykter5, Lotta L. N.J.C. Smith: None. Chronic myeloid leukemia (CML) is myeloproliferative disease, which is successfully treated with tyrosine kinase inhibitors (TKI), however, 20-40% of patients remain resistant to existing therapy. CIP presents clinically as the insensitivity to nociceptive pain and heat, often with anosmia.We report an 8-years-old girl, from an inbred family, diagnosed with CIP, showing absence of pain sensation, diminished temperature sensation, foot burns, normal olfaction, hearing and MRI. Perumal, Asavela O. Conclusions: We report a patient with DDX3X variant and atypical phenotype. Brandão: None. The bladder exstrophy-epispadias complex (BEEC) comprises of a spectrum of anterior midline defects affecting the bladder or urethra. Mezzavila: None. Moreover, the algorithm was employed to identify the pathogenic digenic variants from WES data of three clinical cases for which a single causative mutation was not able to explain their complex traits. Materials and methods: The patient had two consecutive pregnancies with fetuses with short, bent femurs. Introduction: Hemizygous deletions of parts of the X-chromosome are rare and due to the nullisomy for essential genes often incompatible with life. Patraquim: None. Larger case series are however needed to precise the frequency of these vascular complications and to improve our understanding of the link between complement pathway activation and connective tissue alterations observed in these patients. Hall: None. CNV analysis and SNP array revealed a duplication of ~49 Kb in the chromosomal region 20p11.23 encompassing OVOL2, leading to a diagnosis of PPCD1. Conclusion: We found for the first time that genetic polymorphisms at GSS gene are associated with susceptibility to type 2 diabetes and related hyperglycemia through the mechanisms involving decreased antioxidant defense and increased production of reactive oxygen species. The spectrum of ribosomopathies will be extended by reporting the new mutations in the genes on the ribosomal-pathway and by enlightening their reflections on the phenotypes. Speakers Bureau/Honoraria (speakers bureau, symposia, and expert witness); Modest; Novartis, Sanofi Genzyme, Almirall, Merck-Serono. A.A. Abbasi: None. According to the results, 23.3% of women have the AA genotype (high risk of reproductive loss), 76.7% of women had the AB genotype (medium risk). Magzhanov: None. All observed cases were Yakut nationality. Bienvenu: None. E.B. Kuznetsova: A. Introduction: 3MC syndrome is an autosomal recessive disorder encompassing a variable spectrum of abnormalities, among which facial dysmorphisms are characteristic. Vaicekauskaite: None. P02.048.A North Carlina macular dystrophy: phenotypic variability and computational analysis of disease-implicated non-coding changes David J. Laca: None. Syndromic craniosynostosis with a certain genetic cause is more likely to involve multiple sutures or bilateral coronal sutures. Rodan: None. Grudeva-Popova: None. t(11;14) and t(4;14) were detected in 6% and 5% of samples whereas IGH gene rearrangements without these translocations were common: in FISH analysis, any type of abnormal pattern was detected with a rate of 53,7% for both fusion probes. Egeli: None. Al-Obeid: None. KIF4A was also proposed as a candidate gene for congenital hydrocephalus. Hutchinson: None. Introduction: Biallelic pathogenic variants in PRKN, encoding the E3 ubiquitin ligase parkin, lead to autosomal recessive juvenile Parkinson disease [MIM 600116]. One of the main reasons for this heterogeneity is the variety of 10qter region chromosomal deletions summarized into the "10q26 deletion syndrome". Method: The patient was diagnosed with colorectal cancer in December 2017 by iFOBT. Results: A total of 340,913 variants were identified by whole-exome sequencing in the target regions, of which 70.1% were exonic. P19.009.A Clinical consequences of rare variants in cerebral small vessel disease genes in UK Biobank Amy C. Constantin: None. P.N. Valdmanis: None. Melotte: None. Zaki5, Joseph G. J.L. Castañeda: None. Thus, the deletion identified in both sisters was the result of an unbalanced segregation of a balanced maternal rearrangement. Tonin2,3,11, Alexandre Orthwein7,8, Anne-Marie Mes-Masson5,12, Zaki El Haffaf4, William D. Our finding expands the phenotypic presentation of MCAT mutations and the genetic heterogeneity of nuclear LHON-like phenotypes. Downes: None. P18.045.C BGLT3 and BCL11A variants associated with sickle sell disease phenotype in Angolan children Miguel Brito 1,2, Mariana Delgadinho1, Catarina Ginete1, Brigida Santos2,3 1H&TRC - Escola Superior de Tecnologia da Saúde de Lisboa, Instituto Politécnico de Lisboa, Lisbon, Portugal, 2Centro de investigação em Saúde de Angola, Luanda, Angola, 3Hospital Pediátrico David Bernardino, Luanda, Angola. Reported ocular problems are strabismus, amblyopia and refraction errors. V.N. Prokofev: None. We found evidence of linkage for three loci 7q21.11 (HLOD = 3.02), 7q21.13-7q21.3 (HLOD = 3.02) and 7q22.3 (HLOD = 3.09). Conclusion: New developments in the GPAP have contributed to identify hundreds of disease-causing variants in patients with RDs and confirm diagnosis hypotheses through patient matchmaking approaches. Ownership Interest (stock, stock options, patent or other intellectual property); Modest; Illumina. Overall, our findings are similar to previously described phenotypes in YARS and GARS fly models, confirming that phenotype expressivity does not correlate with aminoacylation-activity of aaRS. Furthermore, gluteofemoral fat deposition may show the opposite effect. Decreased inorganic pyrophosphate (PPi) levels have been linked to ectopic mineralization in patients. Himelreich-Peric: None. Lozhkin: None. We propose a rescue mechanism involving the usage of a gained in-frame downstream start codon, which could potentially avoid frameshift and lead to residual enzymatic function. Gladieff: F. Conclusions: PDT supports and resolves intramural medical problems when the clinical significance of the patient's variant is unknown or clinically inconsistent. Segregation analysis is required to confirm their final significance, which is under process. Results: We observed intellectual disability, developmental delay (predominantly for the language), early-onset epilepsy, skeletal manifestations, abnormal gait, characteristic dysmorphism, and a happy/friendly personality consistent with the original description. Mokry: None. Riegert-Johnson: None. Following the ClinGen guidelines, these 31 gene-disease associations can be upgraded from having "limited" evidence to "moderate" or "strong", based on 56 patients. These results were validated with MSIsensor-pro and MANTIS tools with altering the threshold values for classes. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Modest; NIMGenetics. Trabelsi: None. K.H. Tennekoon: None. Patient's satisfaction with tele services were high. Some studies suggest that oxidative stress could be involved in the development of this disease. P15.049.A Integration of genomics and transcriptomics to identify DNA damage defects in PID patients prone to cancer Lynn Backers 1,2,3, Bram Parton1,2,3, Mattias Van Heetvelde1,2,3, Marieke De Bruyne1,2, Kim De Leeneer1,2,3, Anne Vral4, Filomeen Haerynck5, Kathleen B. The disease can be divided into two major groups based on age of onset 1.) late of onset Pompe disease (LOPD) (>12 months); 2.) infant onset Pompe disease (IOPD) (500 families with developmental brain disorders (DBD) between the years of 2013-2020. Ciomârtan: None. During development of GA4GH metadata concepts and schemas - which influenced standards such as the Phenopackets format - cancer specific annotations from Progenetix have informed conceptual requirements and domain-specific mappings. We found a significant enrichment for genes associated with cellular differentiation, developmental processes, and cellular response to stress. Introduction: The highly consanguineous Sudanese population has one of the oldest African genomes with remarkable genetic heterogeneity augmenting the burden of neurogenetic disorders including Hereditary Ataxia (HA). Our results show that VPA upregulate NANOG expression by 2-fold in adult fibroblast. Taken together, our data indicated that protein intake during the life is more important in respect of the patients phenotype than direct effect of different HGD variants on the functionality of HGD protein. Tvorogova1,3, Andrey S. These can occur as distinct syndromes (AEC, ADULT, EEC3, LMS) or has isolated malformations (split-hand/foot malformation and isolated cleft lip/ palate). Spinocerebellar ataxia type 11 (SCA11) is a rare autosomal dominant form of cerebellar ataxia, characterized by an almost pure, progressive cerebellar ataxia, abnormal eye movements and impairment of speech. This 52 bp deletion in the last exon is expected to result in a frameshift with premature termination of protein synthesis. Transgenes were injected into the same landing sites of the fly genome and verified by Sanger sequencing. The endocrinologist monitors the child's growth. Results: The tumor markers, CEA19-9 and CEA, were tested and the results were 5.11 ng/ml and 4.23 U/ml, respectively. Rodriguez Jimenez: None. SpliceAI reached 86% sensitivity and 92% specificity with a threshold of 0.05. It is based on publicly available resources and/or on open-source academic software (e.g. VariantValidator to generate the HGVS nomenclatures). Muiya1, Namik Kaya1, Nduna Dzimiri1 1King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia, Riyadh, Saudi Arabia, 2AlFaisal University, Riyadh, Saudi Arabia. There were 276 Δmirna with interactions specific to either converters or non-converters. Employment (full or part-time); Significant; SeqOne. Hospital UyP La Fe, Valencia, Spain, 8Prenatal Diagnosis. Garitazelaia: None. Shkurat: B. Background: Cystic fibrosis is one the most common autosomal-recessive genetic disorders in the Caucasian population, caused by homozygous or compound heterozygous mutations in the CFTR gene (on the long arm of chromosome 7). Hayrapetyan: None. P18.016.B Direct-to-consumer genetic tests providing health information: A systematic review of consequences for consumers and healthcare services Joshua J. Global development delay, short stature, microcephaly and typical facial appearance with triangular face, large forehead, low-set malformed ears, hypertelorism, prominent nose and a thin vermilion of the upper lip constitute the main clinical features. Although core motor features include gait ataxia and action tremor, some patients demonstrate parkinsonism, cognitive deficits and peripheral neuropathy. Metabolic workup, hearing, abdominal ultrasonography, echocardiography, cranial MRI, chromosomal analysis, microarray analysis and PITX2 sequence analysis were normal. The sex, age and comorbidities data were collected and the genotype distributions of 8 different SNPs in all patients were analyzed. de la Rosa: None. The most frequent manifestations in patients were developmental delay, delayed speech, seizures and brain malformations (corpus callosum hypoplasia, delayed myelination, ventricular dilatation). Symptoms include benign cutaneous fibrofolliculoma, pulmonary and kidney cysts and spontaneous pneumothoraces. The correct genotype was confirmed in collaboration with clinical site at the Unilabs Slovensko, s. With clinical and DNA methylation studies we were able to confidently classify most variants. Data was analysed using SPSS. Conclusions: These data suggest that patients with germline mutations in DNA repair genes are less proficient at repairing the DNA damage induced by asbestos and show increased susceptibility to asbestos-induced MPM. K.S. Amr: None. BirthDefects Res A Clin Mol Teratol 94: 824-840.2. Robinson A, Escuin S, Doudney K,.3. Hospital UyP La Fe, Valencia, Spain, 10Perinatology Research Unit. Ovejero: None. Howe12, Pirro G. However, we observed nominally significant accumulation of non-coding DNMs at bivalent TSS/enhancer chromatin states in nsCL/P during human embryonic face development at Carnegie Stage 15 (p = 0.0269), and a nominally significant enrichment of non-coding DNMs in topologically associating domains at two GWAS risk loci, i.e. 4q28.1 (7 cases, 0 controls, p = 0.0008) and 2p21PKDCC (7 cases, 2 controls, p = 0.0161). Welzenbach: None. Beaumont: None. In 56% of the cases, the consultations were by videoconference, in 56% of the cases for a result report, in 64% of the cases as a replacement for a physical consultation due to the epidemic. van der Crabben2, Elise A. Brisson: None. Employment (full or part-time); Modest; Geneton Ltd. Material and Methods: Retrospective descriptive study of patients with XGS diagnosis at clinical genetics service of Spanish tertiary-level hospital. P11.048.B A new heterozygous c.730T>A, p.(Cys244Ser) variant in TP63 associated with severe hydronephrosis and volar nails Mariana Tomásio Neves, Patricia Dias, Ana B. Mendez: None. For instance, for POGZ, sleep disorders appear much more frequent than epilepsy. Pheatmap (R package) was used for the heatmap diagram; only log2-fold changes with an adjusted p-value of 0.10 were considered significant. Lam: None. Some polymorphisms have a tendency of increasing heterozygosity which may be due to genetic drift or natural selection. By incorporating unique molecular identifiers, this technology reduces overestimation of sample size because of PCR inflation and, consequently underestimation of variance. Conclusion: A GWAS meta-analysis of 724,756 individuals identifies 12 novel loci associated with ARHL while confirming previously reported genes in either mice or humans. Most effective approach to identifying these N-glycosylation disorders is mass spectrometry (MS) using either released glycans, intact glycoproteins or proteolytic peptides as analytes. Auvin: None. We since acquired a mobile trolley with a high definition camera that is placed in the busiest neonatal ward in our region. P04.083.D SHFM3 caused by a duplication involving BTRC but not POLL and with possible modifier variants in FRAS1 and C2CD3 Gökhan Nalbant 1, Aslıhan Tolun2 1Department of Biostatistics and Bioinformatics, Institute of Health Sciences, Acibadem University, Istanbul, Turkey, 2Department of Molecular Biology and Genetics, Istanbul Technical University, Istanbul, Turkey. Also, the link between sperm quality and the chromatin protamination status is known. Mortensen, John McGrath, Bjarni Vilhjalmsson Aarhus University, Aarhus V, Denmark. Results: We correctly detected all genetic variants in men with known genetic aetiology. Introduction: Mandibulofacial dysostosis with microcephaly (MFDM) is a multiple malformation syndrome due to haploinsufficiency of EFTUD2 gene. Results: This study reveals the presence of a variant in PIGK (c.748A>C; p.Thr250Pro) in homozygosity. WES was applied to analyse DNA of the proband and both parents. Methods: In a case-control study, we studied the relationship between the FTO and LPL genes with obesity in 520 children and adolescents of both sexes aged 3 to 17 years: the main group consisted of 370 obese and control - 150 in children and adolescents. Here, we identified nineteen families with an inherited CHD3 variant, likely explaining the proband's phenotype (12 predicted pathogenic missense and 7 predicted loss of function variants). U.A. Kozhamkulov: None. Recently, in another 3-year-old patient with ASD, a genetic study was carried out using a 180K CGH-array, finding a 0.265 Mb deletion in 20p12.1 (chr20: 14776880_15041538) in the MACROD2 gene. Myllärniemi: None. Bilbao: None. Seizures and ataxia were noted in 81.8 and 72.7% of patients, respectively. Genomic studies provide novel molecular targets for obesity treatment by discovering genes and pathways involved in obesity. L.G. Boven: None. We also tested whether a polygenic risk score (PRS) could explain the phenotypic variation. Alfares: None. Prokopenko: None. Here, we aim to define the frequency of pathogenic (P) and likely pathogenic (LP) germline variants in known CPGs in young adults with NET. Clinical diagnosis enables advanced diagnostic methods to be applied in timely manner and informed decisions on prenatal and postnatal care to be made. F.N. Esen: None. Gemelli IRCCS, Rome, Italy, 3University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA, 4National Human Genome Research Institute, Bethesda, MD, USA, 5Utah Valley University, Orem, UT, USA, 6Department of History and Sociology of Science, University of Pennsylvania, Philadelphia, PA, USA, 7Department of the history of biological sciences, Moravian museum, Brno, Czech Republic, 8Department of chemistry and biochemistry, Mendel University, Brno, Czech Republic, 9Mendel Museum of the Masaryk University, Brno, Czech Republic, 10Augustianian Abbey, Brno, Czech Republic, 1112) Department of Genetics and Genomics, Faculty of Medicine and Center of Molecular Medicine, CEITEC, Masaryk University, Brno, Czech Republic. The KMT2D c.6264C>T (p.=) was predicted as benign and probably not involved in RNA splicing, TET2 c.972A>G (p.=) as likely benign and probably involved in it. Results: Our results suggest that bowtie2 performs significantly worse than other aligners and should not be used for medical variant calling. Aldaz: None. The child presented giant hepatomegaly, increase in transaminases (AST 1740 IU/L [T; p.(Ser617Leu)) on TLK2 interactions, localization and activity. Fernandez-Lopez: None. The prospect of a "genomic revolution" as declared by Matt Hancock, the UK's health secretary, announced a plan to sequence the genome of all babies born in a NHS hospital, raises many ethical questions in a broader bioethical context. Progression is consistent with loss of a functional intracellular protease inhibitor. O.A. Shukhov: None. Genetic variants with p-values less than 1e-06 (suggestive threshold) were carried forward for functional

annotation e.g. regulation of nearby genes or spatially close genes. Conclusions: CES/WES data are helpful for investigation of a population and for clarification of the burden and structure of hereditary pathology. In the context of Alzheimer Disease, we propose a family-based methodology to estimate the penetrance of SORL1 rare (allele frequency7]) adjusted for APOE4, the main risk factor (allele frequency ~14%, odds ratios [3.4-14]). P15.039.C Deep, rapid and unbiased plasma proteomics with Proteograph™ enables proteogenomic studies with differential analysis of proteoforms Margaret K. Of note, the genetic contribution is rather high with an estimated heritability of >90%. Kowalski: None. For Yakut we found 9 clusters yielded 7966 PE-genes. P05.031.A A new perspective in the study of genetic basis of hypertrophic cardiomyopathy Elena V. Maniglia, Eny M. Thus, Plasma provides an integrated versatile solution to teach in a user-friendly way realistic bioinformatic analyses, thus better preparing students for their future work in research labs. P06.004.A Mild forms of hypophosphatasia in Northwest Russia, update Mikhail Fedyakov, Y. Results: Multiple frequent variants (MAF: 0.167 [IQR: 0.157, 0.167]), that are mostly absent in imputed genome datasets, show stronger effects on Lp(a) in cases ($\beta = 31.91$ mg/dL [IQR: 28.34, 47.79]). I.R. Martínez-Orga: None. Developments in clinical genetics are increasingly moving towards the possibility of preventive clinical genetics (PCG), opposed to current indication-based paradigms. For CNVs (e.g. CFTRdele 2,3), we achieved >99% accuracy. The girl was diagnosed with a new mutation for the family. Reyre: None. Although CK detection is routinely assessed by chromosome banding analysis (CBA) or chromosomal microarrays (CMA), the obtained results are not equivalent. Vissers*: None. c) Genome wide Tandem Repeat (TR). Conclusions: Less than one case of NPC is diagnosed per year in Quebec which is equivalent to a minimal prevalence of 1,19:100000 births. Then, we calculated a variation constraint metric for regulatory regions and showed that genes controlled by constrained regions are more likely to be disease-associated genes and essential genes. Multiple researchers independently performed a selection process and assessed included studies for methodological quality using the Critical Appraisal Skills Program. We explored the role of LINE1, the largest class of Transposable Elements, in human T-cells. The clinical manifestations and age at onset are highly variable. Conclusions: PGT is a successful reproductive option for couples with NF1. Altmüller: None. Conclusions: CdLS is a heterogeneous clinical and genetic condition. Conclusions: The present study identified a novel missense mutation (c.806T>G, p.I269R) in the HDAC8 gene leading to CdLS, which not only provided strong evidence for diagnosis in this present patient, but also expanded the spectrum of pathogenic mutations for CdLS. L.P. Bruno: None. Early risk detection could reduce the incidence, morbidity, and mortality of the disease. Scheer: None. Liguori: None. Ghebeh: None. Grant: This work was supported by U54HG006504 (Yale Center for Mendelian Disorders, to MG). Results: Cytogenetic analyses were performed on cultured peripheral blood lymphocytes. Results: Cytogenetic studies of 1720 spontaneously aborted fetuses were performed. Fröber: None. The allelic ratio of multiple SNPs is determined by parallel analysis with Deep Amplicon Next-Generation Sequencing of cfDNA. Radaelli: None. Previous functional analyses have supported the pathogenicity of the variant. Introduction: Neoadjuvant chemotherapy (neoCTx) followed by hepatic resection is the treatment of choice of patients with colorectal cancer liver metastasis (CLM). The data are mainly epidemiological and histological, and they do not explain the causes and molecular mechanisms. We identified 186 genes showing evidence for alternative splicing and described the individual events for the first time in osteoarthritis. Almoallem: None. Nonetheless, in the diagnostic setting, it becomes necessary to bioinformatically filter the data, restricting the analysis only to those genes compatible with the phenotype (so called "virtual panels"). Results: We identified a burden of rare variants in genes associated to lysosomal or mitocondrial function in PD patients compared to controls, 45% vs 17% and 76% vs 39% respectively. Individuals in class I have microduplications of the YWHAE, but not PAFAH1B1 and generally, result in learning disabilities, autism, and developmental delays. A whole genome sequencing (WGS) analysis was performed: the library preparation (paired-end 2x150 bp) used the NEBNext DNA Library Prep Kit. Conclution: We consider that problem solution is associated with trinity realization of genome, microbiome and virome, external environment, epigenetic status interaction. Speakers Bureau/Honoraria (speakers bureau, symposia, and expert witness); Modest; BioMarin Pharmaceutical Inc, Shire, Sanofi Genzyme. The most prevalent gene attributing to HCM was MYBPC3 (30%). Introduction: The deficiency of tyrosine hydroxylase leads to autosomal recessive L-DOPA-responsive infantile Parkinsonism and susceptibility to adult-onset L-DOPA-responsive dystonia due to striatal dopamine shortage. Results: All patient fibroblasts had lower rates of maximal respiration, and spare respiratory capacity, while basal and ATP-linked respiration rates were variable, compared to controls. Materials and Methods: The proband was a 6 year-old female with a normal psychomotor development until age 3, when she began to show language regression, slight impairment of eye contact and motor skills. Kolobkov2,4, Alesya S. Here we benchmarked free software tools for variant prioritization of causal variants from empirical WES data. Results: Mapping of all NMAN-causing variants allowed their classification into three structural clusters: a) catalytic pocket; b) dimer interface; c) β-sheet behind the catalytic pocket. Methods: We generated patient-specific iPSCs from fibroblasts from four WBS patients, four DUP7 patients and two controls, which were differentiated to neural progenitor cells (NPCs) and to dopaminergic neurons. Conclusion: This study highlights the utility of parallel tumor-normal sequencing in identifying PGVs causal for CPS in cancer patients who are not necessarily eligible for genetic germline testing. Droplet digital PCR (ddPCR) offers the potential for NIPD using only a maternal sample via relative mutation dosage; however previous reports describe unacceptable rates (up to 10%) of incorrect genotype classifications. Soubrier: None. We perform an in-depth clinical characterization of a cohort of 36 unpublished individuals with SETD1B sequence variants, describing their molecular and phenotypic spectrum. The normal composition of the GAG side chains defines the nature of the PGs and a wide range of biological events. These include: transgenic and knock-in mouse strains expressing human angiotensin-converting enzyme 2 (hACE2) under heterologous gene promoters or the endogenous mouse Ace2 promoter; and common inbred strains transduced with hACE2-encoding adenoviral/adenoviral-associated vectors or infected with mouse-adapted SARS-CoV-2 strains. Results: Exome sequencing revealed heterozygous frameshift variant leading to premature stop codon NM_001356.5:c.1629_1630dupAT (NP_001347.3:p.(Phe544TyrfsTer8) in DDX3X gene. Hence, we sought to decipher the role of TEs in regulating tumour-infiltrating lymphocytes (TILs) plasticity and their impact in the heterogeneity of T cell subsets in the tumour microenvironment. England: A. Parents often chose exome-wide (trio-)analysis over cancer panel analysis, although they faced significant difficulties distinguishing between these approaches. Results: This resulted in 27 dialogues in one year with a broad variety of publics, numerous accounts of dialogues in (social) media and a summarizing report for our Ministry of Health, Welfare and Sports. For instance, RNA-seq provides genome-wide quantifications of expression and is used to understand the consequences of GWAS variants. Case report: Here we report family with aortic dilatation. Variant causes deletion of amino acid (p.Glu157del) located in an important enzyme domain. Jeunemaitre: None. Kamenarova: None. Conclusions: The CPMS project was effective in implementing the platform use, maximizing data sharing among care providers, through virtual panels of discussion. Posey1, Claudia M. Hereditary spastic paraplegias (HSPs) are a large group of neurodegenerative disorders, characterized by lower limb spasticity and weakness, but may include a range of other neurological and non-neurological symptoms. Of these, 7/43 (16.3%) patients had CNVs in the epilepsy/neurodevelopmental disorder "hotspots" (15q13.3, 15q11-q13, 16p11.2, and 16p13.11), and 4/43 (9.3%) patients have at least two potentially causative CNVs. We identified novel CNVs in genes previously implicated in other neurodevelopmental disorders (L1CAM) as well as epileptic encephalopathy (DENND5A). Lenaerts: None. Babovskaya, Ekaterina Trifonova, Maria Swarovskaya, Viktoria Serebrova, Alexei Zarubin, Vadim Stepanov Research Institute of Medical Genetics, Tomsk National Research Medical Center of the Russian Academy of Sciences, Tomsk, Russian Federation. Therefore, the identification of host factors contributing to the variation could introduce new HIV-1 treatment strategies. Material and Methods: We recruited two multiplex Pakistani families, having 11 patients and 19 normal individuals in three generations. Since the mother had normal karyotype and father was unavailable for eventual translocation, array CGH was performed with the presence of major duplication of 7p21.3p11.2 encompassing 46,925 kbp, with 334 genes, estimated as 90% of the cells. LoFTK is command-line based that allows for integration in existing workflows and enables efficient and automated LoF variant and gene prediction. Our results support a reoriented view of several ALS genes and variants. Rogel: None. Esteve Garcia: None. Physical examination, X-ray and DNA analysis were performed. Major challenges in WGS are interpreting and handling the large amount of data and finding the causative variant(s). Gleeson5, Nathalie Boddaert1, Vincent Cantagrel 1 1Institut IMAGINE, Paris, France, 2University College London, London, United Kingdom, 3CHU-Lenval, Nice, France, 4Centre Hospitalier Universitaire de Nice, Nice, France, 5University of California San Diego, san diego, CA, USA. Introduction: Titin is a giant protein encoded by the TTN gene with 364 exons. Results: Eleven independent studies were analyzed with 16,431 subjects in total. Dcx, a marker of neurogenesis and Neurod1, a marker of neuronal differentiation, are expressed at a very low level compared to the fresh hippocampi conditions both in neurospheres and in GalC7 hydrogels. Together, 65 couples underwent 141 PGT cycles and the transfer of 162 unaffected embryos resulted in 39 ongoing pregnancies (pregnancy rate 24,1%/embryotransfer). Introduction: Over the years, Next Generation Sequencing (NGS) workflows have become more and more complex, and they include a variety of sample types such as Formalin Fixed Paraffin Embedded (FFPE) samples and Cell-free DNA (cfDNA). Functional enrichment revealed an overrepresentation of the cell-cell adherens junction and the cadherin-catenin complex, represented by multiple upregulated proteins within this complex, including CDH2/N-cadherin, CTNNB1/ß-catenin, and JUP/plakoglobin. The variants were confirmed by Sanger sequencing. Servicio de Cardiología., Madrid, Spain. This 12bp in-frame deletion lies in exon 6 of NCSTN, resulting in the loss of 4 amino acid residues. Mutation p.E191K in exon 6 is 12 times common in patients with low levels of ALP compare general population. Cortón: None. Bonnet-Dupeyron: None. Materials and Methods: Alignment and variant calling were performed for publicly-available reference datasets (HG001-HG004), while measuring runtime, as well as for ~50 in-house WGS samples (60× PCR-free, PE150) using BWA/GATK, DRAGEN, GENALICE, Isaac/Strelka2, Parabricks (GPU-accelerated BWA/GATK and BWA/DeepVariant), and Sentieon (CPU-accelerated BWA/GATK and BWA/DNAscope). Pappas: None. Ownership Interest (stock, stock options, patent or other intellectual property); Significant; AstraZeneca. This study aims to examine the association between three KLF1 common variants (rs3817621; rs79334031; rs2072597) and HbF and HbA2 levels in β-thalassemia carriers. P22.033.D Telemedicine tools to break down barriers in neuromuscular diseases: Clinical Patient Management System (CPMS) and Telegenetics Fernanda Fortunato 1, Marianna Farnè1, Francesca Bianchi2, Marcella Neri1, Gabriele Siciliano2, Valeria Sansone3, Andrea Barp3, Emilio Albamonte3, Gianluca Vita4, Antonio Atalaia5, Teresinha Evangelista6, Francesca Gualandi1, Alessandra Ferlini1 1Unit of Medical Genetics, Department of Medical Sciences, University of Ferrara, Ferrara, Italy, 2Neurology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, 3NEMO Clinical Center in Milan, Milan, Italy, 4NEMO Clinical Center in Messina (NEMO Sud), Messina, Italy, 5Institut de Myologie, Sorbonne Université- Inserm UMRS 974, G.H. Pitié-Salpêtrière, Paris, France, 6Unité de Morphologie Neuromusculaire; Institut de Myologie, Sorbonne Université-AIM, Paris, France. M.E. Hauberg: None. Independent discoveries were shared through GeneMatcher. Materials and Methods: CHEK2 variants p.Trp114Cys, p.Arg117Gly, p.Ser187Phe, p.Glu239Lys, p.Glu302Lys, p.Met304Val, p.Thr323Pro, p.Ser356Leu, p.Ile364Thr p.Met381Val, p.Ser412Arg, p.Arg474His, p.Thr476Met and p.Asp488Glu were analysed. C.K. Boahen: None. Genetic analysis was based on the approach proposed by Cortese et al. Four patients (median age of 24 years (IQR: 21-27)) presented with TC of which 3/87 had a medical history of TC and 1/75 developed TC during TUS. Pinheiro: None. We demonstrated that NRIP1-MIR99AHG results in overexpression of the 3' region of MIR99AHG and the disruption of the tricistronic miRNA cluster miR-99a/let-7c/miR-125b-2. Materials and methods: 43 undiagnosed patients in which the exome test showed a VUS or a phenotype-genotype incongruity were selected. Grosso: None. Materials and Methods: A 22-month-old male with clinical suspicion of glycogenosis type VI or IX was referred to our laboratory for genetic study of candidate genes by next generation sequencing (NGS). P01.010.B Molecular genetic carrier screening of in the Republic of Sakha (Yakutia) (Russia) Aitalina Sukhomyasova 1,2, Anastasia Danilova1, Tatyana Grigorieva1,2, Lutcia Gotovtseva1,2, Polina Golikova1, Nadezhda Maksimova1 1North-Eastern Federal University named after M.K. Ammosov, Medical Institute, Yakutsk, Russian Federation, 2"Republican Hospital No. 1-National Center of Medicine", Yakutsk, Russian Federation. The novel recessive variant identified in several members of our Brazilian family gives us the unique opportunity to study the functional effect of the C1-INH p.Val322Met variant on the control of the kinin-kallikrein system. Pathway and network analysis indicated close functional connections. Introduction: DNA methylation analysis is an emerging method in the diagnosis and prognostication of neoplastic diseases. Materials and methods: We performed a retrospective analysis of our adenomatous polyposis patient cohort to identify those with biallelic NTHL1 pathogenic variants (PVs). Results: MR analysis revealed significant associations between genetically predicted shorter TL and reduced cortical thickness in age and AD-related brain signatures; however, evidence for directional pleiotropy was observed. Parfait: None. Analysis of the 11 candidate SP genes is currently being performed in further ~100 SP patients, ~100 adenomatous polyposis patients and ~1000 familial/early-onset CRC patients, with the aim of validating our findings in an independent SP series and confirming that the enrichment of Wnt-related variants is exclusive of SP or, at most, of polyposis phenotypes. Methods: The patient was referred with a presumed diagnosis of osteopetrosis for genetic examination. Alekseeva1, Irina V. Conclusions: Germline mutations in cancer associated genes were found in 27% of our patients. Koleva: None. Inan: None. Prenatal lymphatic problems increased the risk of lymphatic problems during infancy (odds ratio 10.5, 95% confidence interval 3.6-30.1). AlMuhaizea: None. This work was financially supported by the Ministry of Science and Higher Education of the Russian Federation (Agreement No. 075-15-2020-901) to Al.K. and Broad Institute SPARC award to M.J.D. and A.M. V. Other Research Support (supplies, equipment, receipt of drugs or other in-kind support); Modest; Novo Nordisk. Minigene assay demonstrated that it is a "leaky" spliceogenic mutation, which leads to approximately 50% reduction of WT transcript isoform. Bächinger: None. Paramonov6, A. Menéndez: None. Various IDs were detected in each group (Table). Materials and Methods: After quality control, genotype data generated as part of the Breast Cancer Association Consortium (BCAC) OncoArray project was available for 184 BRCA1/2 variants. P10.056.D Phenotype in Associated SMA mutations - experience of 5 years Ramona Babici 1, Maria Tonu1, Mihaela Danila1, Doina Ursan1, Roxana Popescu2,3, Lacramioara Butnariu2,3, Monica Panzaru2,3, Eusebiu Vlad Gorduza1,3, Cristina Rusu2,3 1"Cuza Voda" Maternity Hospital, Iasi, Romania, 2"Saint Mary" Emergency Children's Hospital - Regional Medical Genetics Centre, Iasi, Romania, 3"Grigore T. .. López Soriano: None. Maugard: None. Immune system's dysregulation is a key factor in the AD pathogenesis, particularly Toll-like receptors (TLRs) which participate in neuroinflammatory reactions. There were 9 girls and 9 boys aged 3-17 years (mean age 12,1). 46,XY patients show ambiguous genitalia at birth, including perineal hypospadias and a persistent urogenital sinus with a blind perineal vaginal orifice.DSD used to be diagnosed at birth or childhood by pediatricians or within the family, making our case especially unusual. C.W. Alvarez: None. Several issues have to be discussed with patients and families during genetic consultation session, including the option for genetic testing and cardiovascular surveillance in family members. P12.175.C A case of PTEN hamartoma tumor syndrome; a family study Hatice Ilgin-Ruhi 1, Ezgi Gokpinar-Ili2, Naz Guleray Lafci3, Elifcan Tasdelen4, Sule Altiner1 1Ankara University Medical Faculty, Ankara, Turkey, 2Başakşehir Pine and Sakura City Hospital, Istanbul, Turkey, 3Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital, Ankara, Turkey, 4Sanliurfa Education and Research Hospital, Sanliurfa, Turkey. Antunes: None. We have reprogrammed fibroblasts from a trio – two neurotypical parents and their daughter diagnosed with ASD, harboring a de novo 120 kb deletion in SHANK2 – into induced pluripotent stem cells (iPSCs), and subsequently differentiated them into neural stem cells (NSCs). This metabolic defect is characterized by an accumulation of highly phosphorylated inositols, mostly inositol hexakisphosphate (IP6), detected in HEK293, fibroblasts, iPSCs and differentiating neurons lacking MINPP1. De novo CHD3 variants cause Snijders Blok-Campeau syndrome (SNIBCPS; MIM#618205). Methods: A single-center descriptive and retrospective study was carried out based on electronic medical records. Introduction: Vaccinations are one of the most significant achievements of medicine in modern times. P01.012.D Personalised non-invasive prenatal diagnosis (NIPD) for maternally inherited variants in rare conditions using droplet digital PCRJoe Shaw1, Ben Paternoster 1, Maureen Ramos1, Sarah Nesbitt1, Sophie Sheppard1, Lyn S. Umriukhin 1,2, Elizaveta S. Materials and Methods: From 2016 to 2020, hATTR was genetically identified in 95/534 (detection rate 17.8%) patients coming from Northern and Central Italy Centers. These results clearly demonstrate the benefit of incorporating correlated information. Dericquebourg: None. Zeschnigk: None. Jayakar: None. Taylor6, Bruno Dallapiccola1, Fowzan S. Lázaro: None. B.K. Thakur: None. Iglesias: None. Levstek: None. Le Caignec: None. Both parents had normal karyotype. Malfait: None. In addition, we observe highly frequent overlap of breakpoints in samples of the same cancer type. Haploinsufficiency of DLL1, which is a NOTCH ligand, causes a neurodevelopmental disorder with nonspecific brain abnormalities with or without seizures. The average age at the first presentation was 4 years and at the diagnosis confirmation was 4.5 years. Maia: None. Class II-microduplications generally result in smaller body size, developmental delays, microcephaly, and other brain malformations. Lamina: None. O'Donnell-Luria: None. Zeggini: None. Heat shock protein 47 (HSP47), encoded by the SERPINH1 gene, is a molecular chaperone essential for correct folding of collagens. Structural impact of substituted residues was assessed through in silico modelling using iTASSER. Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease, mainly caused by PKD1 and PKD2 genes. Gallo: None. He had long narrow face, bulbous nose, sparse lateral eye brows and strabismus. We aim to present a novel pathogenic variant in PDP1 gene in a pediatric patient. Using European Renal Association-European Dialysis and Transplant Association Registry, and population based studies, Willey et al. P09.009.B Whole-exome sequencing reveals differential enhancement of ion channels activity genes between Alzheimer patients and controls Dimitar Serbezov 1, Maja Atanasoska2, Lubomir Balabanski1,2, Sena Karachanak-Yankova1,3, Radoslava Vazharova4,2, Dragomira Nikolova1, Marta Mihaylova1, Rada Staneva1, Olga Antonova1, Vera Damyanova1, Mihail Ganev1, Viktoria Spasova1, Dessislava Nesheva1, Zora Hammoudeh1, Savina Hadjidekova1, Diyana Belezhanska1, Shima Mehrabian1, Maria Petrova1, Latchezar Traykov1, Draga Toncjeva1 1Medical University of Sofia, Sofia, Bulgaria, 2Gynecology and assisted reproduction hospital "Malinov", Sofia, Bulgaria, 3Department of Genetics, Faculty of Biology, Sofia University "St. Kliment Ohridski", Sofia, Bulgaria, 4Department of Biology, Medical genetics and Microbiology, Faculty of Medicine, Sofia University "St. Kliment Ohridski", Sofia, Bulgaria. Fetal chromosomal abnormality ratio that we found was 7.38%. We found that brain-specific unannotated 3'UTRs were enriched for the binding of important neuronal RBPs such as TARDBP and RBFOX1, and their associated genes were involved in synaptic function and brain-related disorders. NIPT can accurately detect aneuploidies and large chromosomal aberrations in cfDNA in maternal blood plasma. Materials and Methods: Plasmids containing either the wild-type or three mutated forms of Sema6b (V183L, R372* and W689*) were overexpressed first, in HEK293T cell line to assess the impact of the variants overexpression on Sema6b expression, stability and subcellular localization and then, in primary neuronal cultures to characterize the effect of the variants on morphogenesis and synaptogenesis. Methods: A ddPCR assay was designed for the common SCD variant, HBB c.20A>T, and validated on heterozygous genomic DNA and paternal cell free DNA. M.P.A. van Koolwijk: None. Colak: None. G.I. Elchinova: None. Mansour: None. Substantial advances in the ability to detect genetic variation, at speed and low cost, together with the need to make these advances available to a much wider range of healthcare professionals - via the NHS Genomic Medicine Service - means that consideration of the ethical issues raised is timely. H.R. Stagg: None. We developed TISSUE (TIssue Specific Screen Using Expression) -informed collapsing analysis, an approach that uses tissue-specific gene expression data from the GTEx database to identify and filter out isoforms found at low levels or unexpressed in the disease-relevant tissue prior to collapsing analyses. Results: Searches through Pubmed and EMBASE resulted in 451 and 608 publications, respectively. Barton: None. Pereira: None. A.M. van Eerde: None. Ten papers reported that P. A colony formation assay was performed to determine the metastatic effect of drugs on cells. The results showed that although there is evidence of childhood BMI affecting most of the reviewed mediators, only IGF-1, testosterone, age at menarche and menopause, and mammographic density have an effect on breast cancer risk. Stavrikj: None. E.A. Fonova: None. Sabaliauskaite: None. van den Berg5, Marc T. Whether both genes contribute to the condition has not been elucidated. Genetic predisposition plays an important role in the development of obesity, but the relationship between obesity loci and gene polymorphisms associated with cardiometabolic disorders in the child and adolescent population has not been established. A.K.M. Nielsen: None. We performed intersection, colocalization of our GWAS results with appendicitis and CRP-associated loci from the Pan-UKBB cohort. Sanger-seq showed loss of heterozygosity at the variant level in all analyzed tumors. An early medical and dietary management was commenced for this first Saudi baby diagnosed with homocystinuria by universal NBS. Some HPs perceive consumer/patients' understanding of genetics and trust in genetic professionals could be compromised by DTC-GT. Rapid whole genome sequencing (rWGS) has a positive impact on care by reducing the need for multiple diagnostic tests and facilitating treatment decisions. Over: None. o. In two cases, the causality of the variant was discarded based on non-segregation or an alternative diagnosis. L.M. Pires: None. P11.045.C New case of Dyskeratosis congenita 4 mimicking Hoyeraal-Hreidarsson syndrome with novel TERT gene mutation Ece Çepni 1, Sahin Avci2, N. Nolan 1,2, Elizabeth Ormondroyd3,4 1Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom, 2University of Manchester, Manchester, United Kingdom, 3University of Oxford, Oxford, United Kingdom, 4Oxford Biomedical Research Centre, Oxford, United Kingdom. To date, clinical features have been described for eleven patients with (likely) pathogenic SETD1B sequence variants. Zanetti: None. P02.059.D Implementation of the targeted retinal dystrophy panel in the routine genetic diagnostics of retinal disorders in Polish patients Ewa Matczyńska 1,2, Przemysław Łyszkiewicz1, Anna Wąsowska1,2, Robert Szymańczak1, Ewa Suchecka1, Katarzyna Stradomska1, Marta Beć1, Maria Jędrzejowska1, Sławomir Teper2, Maciej Krawczyński3, Anna Boguszewska-Chachulska1 1Genomed S.A., Warsaw, Poland, 2Chair and Clinical Dept. Though mutations in each gene are relatively rare, several genes involved in charging and modifications of tRNA molecules have been found mutated in ID-patients. Table. Kavčič: None. Haseeb: None. P12.110.B Prognostic evidence of LEF1 isoforms in childhood acute lymphoblastic leukemia Yucel Erbilgin 1, Ozden Hatirnaz Ng2, Sinem Firtina3, Fulya Kucukcankurt1, Zeynep Karakaş4, Tiraje Celkan5, Sema Aylan Gelen6, Khusan Khodzhaev1, Müge Sayitoglu1 1Aziz Sancar Institute of Experimental Medicine, Istanbul University, Istanbul, Turkey, 2Acibadem Mehmet Ali Aydinlar University, Istanbul, Turkey, 3Istinye University, Faculty of Art and Science, Istanbul, Turkey, 4Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey, 5Istanbul University-Cerrahpasa Faculty of Medicine, Istanbul, Turkey, 6Faculty of Medicine, Kocaeli University, Kocaeli, Turkey. P09.030.C The complexities of CACNA1A in clinical neurogenetics Marina P. Introduction: SPOP encodes a substrate-binding subunit of a Cullin-based E3 ubiquitin ligase, which acts as a tumor suppressor by proteasomal degradation of oncogenic targets. Furthermore, we found impaired electron flux between CI and CIII in skeletal muscle and fibroblasts of the patient. Pagano: None. Conclusions: The information of the functional impact of the analysed fourteen CHEK2 variants will help to establish their clinical significance in cancer patients. Kroes 1, M B. H.L. Sczakiel: None. Background: Genetic services are rapidly growing in many Islamic countries, leading to more diagnoses. Ryzhkova: None. Introduction: Analyzing whole genome sequencing of nearly healthy individuals allows assessing inherited diseases occurrence frequency in different populations. Until recently, GRS was constructed using information on the disease itself; however, as the human genome has abundant pleiotropy the accuracy of risk stratification may be improved by constructing multi-trait (MT) GRS. de Waele: None. In this study, we describe three unrelated families who carried different GUCY2D-variants and presented two types of retinopathy. GBA1 is considered one of the major genetic risk factor for PD. Materials and Methods: DNA from 629 unrelated control donors were sequenced by commercial whole-exome enrichment capture kits and a HiSeq 4000 (Illumina) using 75 bp paired-end reads. Other types of identified variants included small insertions (12.5%), missense (11.36%), splicing (7.95%), gross deletions (3.41%) and small indels (1.14%). Da Costa: None. Medina1 1Department of Pediatrics, University of California San Francisco, San Francisco, CA, USA, 2Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA, 3Department of Pathology, University of California San Francisco, San Francisco, CA, USA. Grimbacher: None. Regarding novel rare variants, we uncovered 453 in 34 PharmGKB Very Important Pharmacogenes. Conclusions: To our knowledge, this is the second report of a medulloblastoma in a patient with NF2 and the first where genetic analysis was performed. P14.031.D Investigation of a de novo complex intrachromosomal X chromosome rearrangement in a girl with primary amenorrhea Voula Velissariou BIOIATRIKI HEALTH GROUP, ATHENS, Greece. Barel: None. Then MTHFR (C677T) genotyping was conducted with Allele-specific PCR to confirm meta-analysis result in FGR-diagnosed (n = 26) and healthy (n = 37) pregnant women. Granger: None. Abasov: None. Materials and methods: We performed a WES study through a trio approach (SureSelect Human All Exon V6 technology) in a HiSeq 4000 platform (Illumina, San Diego, CA). A total of 8635 amniocentesis specimens were processed during the study period. Reuter1, Steffen Uebe1, Mary-Alice Abbott2, Syed A. In childhood, he presented mild DD, language delay and learning difficulties. Petrovic: A. Spector: None. EIP, MEM, and RMR are recipients of National Council for Scientific and Technological Development (CNPq) productivity fellowships. Polygenic risk scores (PRS) provide an aggregate score of variants that have been shown to be associated with a specific disease in GWAS. Materials and Methods: Using PacBio highly accurate long-read (HiFi) sequencing, coupled with a long-PCR targeted enrichment method, we investigated two important dark region genes that are challenging to accurately type with short-read sequencing due to associated pseudogenes: CYP21A2, responsible for congenital adrenal hyperplasia, and GBA, responsible for Gaucher disease. A multigene panel included coding sequences of 882 cancer-associated genes. NGS was used to analyze 52 genes responsible for hereditary diseases with cholestasis. Introduction: Diagnosing rare diseases (RD) is challenging for doctors in many countries, especially in underdeveloped low-income countries like Georgia. The goals of the program are to determine, in pediatric epilepsy patients between 2-5 years of age, molecular diagnostic yield and the impact on diagnosing neuronal ceroid-lipofuscinosis type 2 (CLN2). Baranov D.O. Ott Research Institute of Obstetrics, Gynecology and Reproductology, St. Petersburg, Russian Federation. Introduction: Evidence of the functional legacy of archaic hominids in modern humans is still limited to a few genes and phenotypes. Tan: None. However, omics types are often analyzed in separate analyses and combined afterwards. Our manuscript adds to the limited data on Aarskog-Scott syndrome, and emphasizes the importance of unbiased comprehensive genetic testing towards establishing a diagnosis for genetic associations. Introduction: Mitochondrial disease is one of the most common metabolic diseases with a minimum prevalence of greater than 1 in 5000 in adults. The majority of the mutated genes belongs to 4 biological pathways or regulate them: RAS/MAPK (e.g. FGFR3, PTPN11), Wnt/ß-catenin (e.g. DDX3X,GRIN2A, GRIN1), Sonic Hedgehog (e.g. B9D1,C2CD3) and GPCR signaling (e.g. DDX3X, MKS1). MRI identified lissencephaly type 1, prevalently in the temporo-occipito-parietal regions of both sides with "double-cortex" (Dobyns' 1-2 degree) periventricular band alterations. All of these variant data are stored in organism-specific databases, but finding equivalent variants called orthologous variants (OrthoVars) between organisms remains difficult. Administration via nanomicelle technology. Multiplex PCR is most reliable and cost-effective method for TCR library preparation. One recent study has observed a higher frequency of aneuploidy in heterozygous, compared to homozygous diploid androgenetic hydatidiform moles (Scientific Reports (2020) 10:17137). Quantitative reverse-transcription polymerase chain reaction was used to assess the expression of GNAS. Richmond: None. Methods: The TNBC cell lines were represented by MDA-MB-231 and Hs578T, while MSCs were primary cell cultures. of Pediatrics, Academic Medical Centre, Amsterdam UMC, Amsterdam, Netherlands, 15Department of Human Genetics, Radboud University Medical Center, Nijmegen, Netherlands, 16French Angelman Syndrome Organisation, Paris, France, 17Valentin Organisation for Carriers of Rare Chromosome Disorders, Paris, France, 18Department of Urology, University of Rennes, Rennes, France, 19Department of Surgery, Urology and Neuro-Urology, Bambino Gesù Pediatric Hospital, Rome, Italy, 20Reference Centre for Rare Diseases, Rare Intellectual Disabilities and Multiple Disabilities, CHRU de Brest, Brest, France, 21DéfiScience National Coordinator, Hospices Civils de Lyon, Lyon, France, 22Neuropediatrics Department, Hospices Civils de Lyon, Lyon, France, 23Swedish national Federation for children and youth with disabilities (Rörelsehindrade Barn och ungdomar), Solna, Sweden, 24Genetics and Rare Diseases Research Division, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy, 25Department of Clinical Genetics, Copenhagen University Hospital, Rigshospitalet, Denmark, 26Vilnius University Hospital Santaros Klinikos, Santariskiu 2, LT-08661, Vilnius, Lithuania, 27Dept of Human Genetics, Radboudumc, Nijmegen, Netherlands, 28Donders Institute for Brain, Cognition and Behaviour, Radboudumc, Nijmegen, Netherlands, 29CERCRID, UMR 5137 "Centre de Recherches Critiques en Droit", Université de Lyon, Lyon, France, 30Institute of Human Genetics and Anthropology, Heinrich Heine University Düsseldorf, Düsseldorf, Germany, 31Department of Woman and Child Health, Center for Rare Diseases and Birth Defects, Institute of Pediatrics, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy, 32Med Biotech Hub and Competence Center, Dept of Medical Biotechnologies, University of Siena, Siena, Italy, 33Medical Genetics, University of Siena, Siena, Italy, 34Genetica Medica, Azienda Ospedaliero-Universitaria Senese, Siena, Italy, 35INSERM UMR 1141 "NeuroDiderot", Hôpital Robert Debré, Paris, France. Platzer: None. E.A. Kamenec: None. Eventually, ARFGEF1 should be routinely screened in unsolved cohorts of individuals presenting with neurodevelopmental disorders with or without epilepsy. P05.019.A Role of xenobiotic biotransformation genes in genetic predisposition of congenital heart diseases Anna Tsepokina, Svetlana Shmulevich, Anastasia Ponasenko, Andrey Shabaldin Research Institute for Complex Issues of Cardiovascular Diseases, Kemerovo, Russian Federation. Baldewijns: None. Madej-Pilarczyk: None. Introduction: Dedifferentiated liposarcoma (DDL) is considered a well-differentiated form of histological (tumor) progression of liposarcoma. Brambilla: None. Iwanicka-Pronicka: None. Moreover, weidentify putative region-specific selection signals associated to environmental factors. P20.016.C C-terminal truncation of NR2B subunits of NMDA receptor - functional characteristics of the GRIN2B nonsense mutation p.Glu839Ter Roza Szlendak 1,2, Nathalie Bouquier2, Annie Varrault2, Tristan Bouschet2, Eymeline Pageot2, Sylwia Rzońca-Niewczas1, Dorota Hoffman-Zacharska1, Julie Perroy2 1Department of Medical Genetics, Institute of Mother and Child, Warsaw, Poland, 2Institute of Functional Genomics, IGF, University of Montpellier, CNRS, INSERM, Montpellier, France. Phenotypic data recorded included all clinical characteristics: abnormal growth, facial, cardiac, thorax, and other features: learning difficulties, ocular anomalies, cryptorchidism, and disorders of pubertal timing, lymphatic anomalies. Noroozi: None. P04.050.C Novel variant in SMAD3 gene associated with Loeys-Dietz syndrome type 3 Albertas Valintėlis 1, Marius Šukys1, Eglė Ereminienė2, Inga Nasvytienė1, Lina Basel-Salmon3,4,5, Rasa Ugenskienė1 1Department Of Genetics And Molecular Medicine, Lithuanian University of Health Sciences, Kaunas, Lithuania, 2Department of Cardiology, Lithuanian University of Health Sciences, Kaunas, Lithuania, 3Raphael Recanati Genetics Institute, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel, 4Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel, 5Laboratory of Immunology and Genetics, Felsenstein Medical Research Center, Petah Tikva, Israel. Although exploratory, this study suggests that such association may result from a protective FMR1 AGG interspersion pattern-related effect or unknown X-chromosome-linked anomaly that likely correlates with female infertility. Results: All affected individuals, originating from Iraq, Syria, Afghanistan and Georgia, suffered from mild hypotrichosis to severe alopecia. te Paske2, José García-Peláez3,4,5, Andreas Laner6, Elke Holinski-Feder6,7, Verena Steinke-Lange6,7, Sophia Peters1, Laura Valle8, Isabel Spier1,9, Solve-RD consortium, Carla Oliveira3,4,5, Richarda M. He was operated for VSD at the age of two. van Kempen: None. EdU incorporation on lymphocytes culture and FISH analysis were used to asses skewed X-inactivation patterns. Soldatov: None. Yiangou: None. Results: Interestingly, the answers of MPs and P&Cs were different. Our aim was to evaluate the association of uEVs and their cargo as possible early biomarkers of FN. Conclusions: The differences in allele and genotype distribution between two extreme age groups of the Croatian population open a possibility that the G allele of the MRE11A gene rs533984 locus might contribute to positive age-related selective survival. M.A.M.S. Bezerra: None. Fernández-Montaño1 1INGEMM, IdiPAZ, Hospital Universitario La Paz, Madrid, Spain, 2CIBER de Enfermedades Raras (U753), ISCIII, Madrid, Spain, 3Dept. Emini: None. Conclusions: The investigated variants of the IL-6 and VDR genes may be the genetic predictor of morbidity and lethal outcomes in patients with COVID-19. MPM is supported by the Raregenomics network (S2017/BMD-3721). Hanein: None. Results: MET pathogenic variant rate among index-cases was 10.4% (16/153) with 37,5% of familial PRCC1 and 3.3% of sporadic PRCC1. Chouk: None. Macroglossia was observed in 39 patients (78%), lateralized overgrowth in 30 (60%), omphalocele in 9 (18%) and prolonged hyperinsulinism in 1 (2%). However, whether correlations exist between PPi levels and the phenotype or ABCC6 genotype is unknown. Taken together, we designed a statistic that harness information of CNV segment breakpoint, to delineate the importance of genetic elements covered by CNV segments. Results: We evaluated molecular genetic results from 835 individuals (461 males, 374 females) from 824 families, including 58 deceased patients who underwent molecular autopsy. We report a rare case of DS due to a balanced maternal t(6;21)(q13;q22). Pužar Dominkuš: None. C.S. Manning: None. Our genetic findings in this family could be consistent with the occurrence of MLID in the proband secondary to maternal biallelic PADI6 mutations (which would imply an increased recurrence risk). Genetic and environmental factors influence complex phenotypes in humans; but they are difficult to identify. The association results were adjusted for covariates (age, sex, BMI, diabetes duration, median HbA1c, and prescription drug use) and a genome-wide significant threshold of P G variant observed in apparently unrelated individuals was indeed inherited from a founder ancestor. Karadima: None. This information may help understand the role of dystrophin in brain co-morbidities observed in affected DMD patients. No effect on the expression levels of TFAP2B was detected for the two Char missense variants. J.D.H. Jongbloed: None. Compound heterozygosity with 4925G>A (4.6%) lowers Lp(a) by 41.6 mg/dL. Mendicute: None. To interrelate perturbed WNT signaling control and germ cell differentiation, we profiled expression levels of canonical WNT ligand, WNT6 and WNT inhibitors, WNT5B and WIF1. Lepage: None. This work was supported by RSF grant 20-75-10091. These data support further clinical investigation into the utility of insomnia treatment as a strategy for pain management and vice versa. The parents embarked on a long and expensive diagnostic odyssey, including CMA and trio WES testing returning no result. Riffo-Ramos3, Belen Sanchez-Garcia1, Daniel Perez-Gil4, Fernando Martinez5, Felipe Chaves1, Josep Redon1, Raquel Cortes1 1Biomedical Research Institute Clinic Hospital - INCLIVA, Valencia, Spain, 2INSERM, U1016, I, Cochin Institute, Paris, France, 3Universidad de La Frontera, Temuco, Chile, 4Genomics England, Dawson Hall, Charterhouse Square, London, United Kingdom, 5Medical Research Institute La Fe Hospital, Valencia, Spain. Patients also exhibit cutaneous BAP1-inactivated naevi (BIN), the frequency of which is unknown. Armirola-Ricaurte: None. Öfner: None. Zweier: None. To accommodate more flexibility, we explored variance-component testing via SKAT using PRS-weighted linear kernels. P04.084.A Is Xlαs associated with short stature? Gérard-Blanluet: None. L.L.P. Ramos: A. These protein-altering variants (p.Gly146Ser in FURIN; p.Arg261His and p.Ala494Val in PLG; p.Asn54Lys in PRSS1; p.Arg52Cys, p.Gly54Asp and p.Gly57Glu in MBL2; p.Arg47Gln, p.Ile99Val and p.Arg130His in OAS1) may have predictive value for inter-individual differences in the response to the SARS-CoV-2 infection. Mantere: None. N.J. Lench: A. Conclusions: The relationship between the gene FTO rs9939609 polymorphism and obesity was revealed. Results: These 249 patients with SGA-SS were classified into the SRS-compatible group (n = 148), non-SRS with normocephaly or relative macrocephaly at birth group (n = 94), and non-SRS with relative microcephaly at birth group (n = 7) according to NH-CSS. Conclusions: In our cohort, select international testing criteria identified 1200 ABCA4 variants cause Stargardt disease making genotype-phenotype correlations difficult. This work was supported by the Russian Foundation for Basic Research (20-04-00464) and the Ministry of Education and Science of the RF (project 0259-2021-0009/AAAA-A17-117092070032-4 and the 5-100 Excellence Program). Cremers1, Susanne Roosing1, Helger G. M.M. Rudenok: None. Using ESRseq we proved that pseudoexons were significantly enriched in enhancer regulatory elements, although they were more abundant in canonical exons. CGH showed an unbalanced genome with multiple gains and losses namely, loss of 22q11.2-q13. Conclusion: Y-chromosome cytogenetic and molecular-genetic aberrations were found in 4.4% of infertile men. Talim: None. I.O. Sadovnychenko: None. M.A. Haniffa: None. Only those AML-KMT2A-r cases were enrolled in the study in which FISH revealed atypical t(10;11) (n = 4) and in which FISH positive 11q23 rearrangement was not confirmed by reverse transcription-PCR (RT-PCR) (n = 3). Single deletion was found in 37.7% (common deletion in 41.1%), whereas multiple deletions in 8.4%. In five patients, WES revealed a combination of two in cis polymorphisms that are in trans with another TYR deleterious mutation: this triallelic genotype, already known to explain missing heritability in some OCA1B albinism patients, is likely to explain also part of FVH patients. Introduction: Merosin-deficient congenital muscular dystrophy (LAMA2-RD) is a neuromuscular disorder caused by mutations in the LAMA2 gene, coding for the alpha-2 subunit of laminin-211 (merosin). M.D. Ruiz: None. o., Bánská Bystrica, Slovakia, 3Mendel University in Brno, Department of Chemistry and Biochemistry, Brno, Czech Republic. ITSN1 showed a high intolerance to inactivation reported by GnomAD database with an associated pLI (probability of loss-of-function intolerance) score of 1. Castaño: None. B.E. Gutiérrez-Amavizca: None. Results: 105 loci were associated with AD risk, while 30 additional loci were associated with biomarker levels in body fluids or neurologic features. Notably, six patients had confirmed neurogenic bladder, with one further patient having possible neurogenic bladder that had not been investigated. Overall survival (OS) was inversely correlated with the break in LRP1B gene. Employment (full or part-time); Modest; Samitivej Srinakarin Hospital, Phyathai 2 Hospital, Bumrungrad Hospital, Jetanin IVF, Panthupark Genetics Clinic. Sanchini: None. Pittalis1, Tommaso Pippucci1, Alberto Magi3 1U.O. Genetica Medica, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, 2Dipartimento di Medicina Sperimentale e Clinica, Università degli Studi di Firenze, Firenze, Italy, 3Dipartimento di Ingegneria dell'Informazione, Università degli Studi di Firenze, Firenze, Italy. In Greek patients with ataxia, although the most common SCAs have been studied by our group, the occurrence of FXTAS has not been previously investigated. Nguyen1,7, Martine Tétreault1,2 1Département de Neurosciences, Université de Montréal, Montreal, QC, Canada, 2Centre de Recherche du CHUM, Montreal, QC, Canada, 3Département de Microbiologie, Infectiologie et Immunologie, Université de Montréal, Montreal, QC, Canada, 4Faculté de médecine et des sciences de la santé, Université de Sherbrooke, Sherbrooke, QC, Canada, 5Groupe de recherche interdisciplinaire sur les maladies neuromusculaires, Centre intégré universitaire de santé et de services sociaux du Saguenay-Lac-St-Jean, Saguenay, QC, Canada, 6Clinique des maladies neuromusculaires, Centre intégré universitaire de santé et de services sociaux du Saguenay-Lac-St-Jean, Saguenay, QC, Canada, 7Pediatric Neurology, CHU Sainte-Justine, Université de Montréal, Montreal, QC, Canada. Fronkova: None. J.S. Bhangu: None. P05.010.D Congenital heart defects in Noonan syndrome and PTPN11 muta□onCongenital heart defects in Noonan syndrome and PTPN11 mutation Laura Claudia Popa 1, Nicoleta Andreescu1,2, Simona Farcas2, Adela Chirita-Emandi1,2, Maria Puiu1,2 1Louis Turcanu Children Hospital, Timisoara, Romania, 2Victor Babes University, Timisoara, Romania. Genome editing using a paired gRNA CRISPR/Cas9 system showed the deletion of the target CRE. Lyahyai: None. The thoracic scan identified the pulmonary lesion as an azygos lobe. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Significant; Russian Foundation for Basic Research, Russian Science Foundation. Ramalho: A. Six carriers had 1-2 tumors, one had 3 tumors, and one had 5 primary tumors. In-vitro assays were performed by transient transfection into HEK293 and/or ARPE19 cell lines. Fallah: None. ClinVar archive and Deafness Variation Database were used to generate a list of clinically significant sequence variants in these three genes, as well as GJB2 gene, and estimation of the frequency of sequence variants was performed. Both had heterochromia iridis as additional finding. Here, we present a new case of ZTTK syndrome aiming to contribute to its clinical and mutational spectrum characterization. Macchiaiolo: None. In 22% of patients, the presence of two or more signaling mutations with different variant allele frequencies was detected, which may reflect the complex clonal structure of tumor substrate. Of particular interest, peptides based on adrenocorticotropic hormone (ACTH) and tuftsin are used as drugs to prevent the effects of cerebral ischemia and stress. P12.166.B Detection of PIK3CA mutations in breast cancer: comparison of next-generation sequencing and Sanger sequencing Maria Michelli, Eirini Roupou, Ilenia Chatziandreou, Alexandros Zougros, Angelica A. We searched for "GRIN mutations" as targeted study. Carecchio: None. Krawitz: None. Another case presented compound heterozygous variants in OCA2. Fumet: None. CMA and WES were done on Affymetrix 750K and on Ion Torrent S5 platform (Thermo Fisher Scientific), respectively, while Sanger sequencing used BigDye Terminator kit. Gezsi: None. Tuominen: None. Employment (full or part-time); Significant; Biogen. K.M. Riedhammer: None. Bengoa: None. SNP-a was performed on 37 postnatal cases in 2020 to identify the genetic etiopathogenesis of congenital/neurodevelopmental anomalies by Illumina CytoSNP v12. Coşkun: None. Basically, we were consulted with the complaint of speech delay. Heales1, Sharon Savage1,2, Chia-Ling Kuo3, George A. Gauthier: None. Results: The proband had severe microphthalmia, microcephaly, skeletal dysplasia (bell-shaped thorax, short and angel shaped epiphyses of hands and feet), midface retrusion, short columella, depressed nasal bridge, everted lower lip, and a single central incisor. After three months of surgery (January 2020), we noted the same mutation but the mutation rate was increasing to 0.99%. Rocha: None. Materials and methods: We examined case level genetic evidence (variant frequency in population and co-segregation with diabetes) for all published variants in BLK, KLF11 and PAX4. Target enrichment was carried out using Nextera Rapid Capture Custom Enrichment Kit. Carazo1, N. P08.035.A Multiple major anomalies and microcephaly predict the detection of pathogenic copy number variations in patients with moderate and severe global developmental delay/intellectual disability Jelena Ruml Stojanovic 1, Marija Mijovic1, Aleksandra Miletic1, Brankica Bosankic1, Hristina Petrovic1, Goran Cuturilo1,2 1University Children's Hospital, Belgrade, Serbia, 2Faculty of Medicine, University of Belgrade, Belgrade, Serbia. Orsola-Malpighi Hospital, Bologna, Italy, 5University of Milano U.O.C. Audiologia/Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Italy. Data were analysed in online mode, using NanoGLADIATOR. P11.024.B Are miR-548 family members potential genetic drivers of CAKUT Kristina Mitrovic, Ivana Kolic, Ivan Zivotic, Jelena Filipovic Trickovic, Ana Djordjevic, Maja Zivkovic, Aleksandra Stankovic, Ivan Jovanovic Institute of Nuclear Sciences "Vinca", Belgrade, Serbia. Stoddart: A. Bowers2, Andrew J. Early Onset High myopia (eoHM) (−6.00 diopters or less) is one of the leading cause of vision loss or even irreversible blindness with pathologic complications such as myopic retinopathy, maculopathy, retinal detachment, cataract or primary open-angle glaucoma that is present before the age of ten. To our knowledge, these cases represent the first molecular confirmed SHS patients in Portugal. Notably, this patient has mitochondrial disease criteria score of 6 indicating probable mitochondrial disorder. 7 novel mutations were detected. Shaw: None. Hérissant: None. Matoso: None. Accumulation of acyl-CoA intermediates can inhibit ACSM2B leading to a reduction in mitochondrial energy production.Funding: National Research Foundation of South Africa (NRF), Grant No 117890. Identified patients should preferentially be selected for expedited genetic diagnostics yielding molecular diagnosis within a few days in comparison to several weeks when conducted in a routine clinical setting. Autosomal dominant Robinow syndrome 3 (DRS3, OMIM 601368) is a rare skeletal dysplasia syndrome characterized by dysmorphic features resembling a fetal face, short stature, mesomelic limb shortening, vertebral and hand anomalies. These 12 might contribute to the pathogenesis of COPD, furthermore two genes IRAK2 and MECOM displayed a critical role in the development of lung cancer in patient with COPD. P22.014.A Identification of familial risk of cardiovascular disease: creating expert-based family criteria for the general populationTetske Dijkstra1, Lieke M. The clinical features and laboratory findings of patients were obtained from their hospital records. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Significant; Russian Science Foundation (Grant number 19-14-00268). Chung 1,3 1University of Hong Kong, Hong Kong, Hong Kong, 2Queen Mary Hospital, Hong Kong, Hong Kong, 3The Duchess of Kent Children's Hospital, Hong Kong, Hong Kong, 4London School of Economics and Political Science, London, United Kingdom. In our study, a brother and sister from non-consanguineous parents suffered severe prenatal cerebral hemorrhages. Neurological examination showed axial hypotonia, peripheral hypertonia and increased deep tendon reflexes. Mais Omar: None. Early detection of mutations using liquid biopsy could be used as a novel and highly sensitive tool for monitoring cancer progression. Young: A. Mikhailova: None. Introduction: Continuously growing request for Next Generation Sequencing (NGS) drive the automatization of processes from primer design to variant calling and interpretation. This study is a part of the ANELGEMIA project, which has received funding from the Research Council of Lithuania (LMTLT), agreement No. S-MIP-20-34. The STAP1:NM_012108.3:c.35G>A:p.(Arg12His), was conserved, and the in silico predictors showed damage. The historical samples were collected from excavations at 13 locations, the present-day dataset contains samples from 99 locations, evenly spread across the country. However, our understanding of SHOX-related pathways is still incomplete. Here, we combined both aspects to study the role of the miRNA gene methylation in HM. Molecular diagnosis was reached in 115 (41.1%) families, mainly due to de novo mutations (92/115, 80.0%). We hypothesize that these trends will be maintained and our findings will be further supported by the sample (n = 68) we intend to recruit to ensure power for statistical and clinical significance. Chambon: None. Gaslini, Genova, Italy, 5Italian Institute of Technology, Genova, Italy. Santos: None. de Jong3, Fonnet E. P19.062.B The Dutch Y-chromosomal landscape from theEarly Middle Agesto present day Eveline Altena 1, Risha Smeding1, Eileen Vaske1, Paul Reusink1, Oscar Lao2,3,4, Kristiaan J. This study was supported by KTIA_13_NAP-A-III/6; KTIA_NAP and with the FIKP program. This led to the inclusion of SCN9A on epilepsy gene panels globally. Two different distance scores were calculated; the first one was determined in comparison with the other samples in the same run, whereas the latter was compared to a global database which contains more than 400 clinical samples. Sloan-Bena: None. J.B.J. van Meurs: None. The majority of individuals have vascular changes on neuroimaging. Bocharova: None. They have overlapping clinical findings and they are usually inherited autosomal dominantly. Rajan: None. Several pathologies are caused by pathogenic variants in the TTN gene and constitute a heterogeneous group of diseases. P06.039.D Novel FARS2 variants in patients with early onset encephalopathy with or without epilepsy associated with long survivalGiulia Barcia, Marlene Rio, Zahra Assouline, Coralie Zangarelli, Charles-Joris Roux, Pascale de Lonlay, Julie Steffann, Isabelle Desguerre, Arnold Munnich, Jean-Paul Bonnefont, Nathalie Boddaert, Agnès Rötig, Metodi D. Introduction: Mutations in RMRP, a nuclear encoded, intronless gene, can lead to the autosomal recessive, multi-systemic disease cartilage-hair hypoplasia (CHH). S.M. Berger: None. Interestingly, one Bulgarian patient with axonal CMT also experienced pyramidal and cerebellar symptoms. We also analysed how these motives were related to various characteristics of the participants and their intention to permit data linkage to their personal data for research. This publication is part of a project that has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825903. In this study, we aimed to fully characterise the clinical and molecular aspects of two Saudi probands who were diagnosed early with Usher syndrome. Inyushkin, Elena S. A homozygous variant (nonsense substitution) in the C19orf12 gene, (p.Leu72) Chr19(GRCh37):g.30193863A>C, was identified through WES. Lobo: None. We have selected a subset of LSDs based on the availability of specific enzyme replacement therapy: Pompe disease (GAA gene), Fabry disease (GLA gene), Gaucher disease (GBA gene) and Mucopolysaccharidosis Type I (IDUA gene). But there is much more to his life and work to be seen following his path from a small birth town, to a monastery in Brno, a university in Vienna, political activism in Brno, and, of course, his experimental garden and bee house at the Augustian monastery (mendelmuseum.muni.cz/en). P15.033.A Monitoring circulating tumor DNA predicts cancer recurrence by using liquid biopsy in a colorectal cancer patientChia Cheng Hung1, Hwei Ming Huang2, Tze Kang Lin1,3, Chieh Wei Huang4, Chang Wei Yeh4, Yi Ning Su 1,5 1Sofiva Genomics, Co., Ltd., Taipei, Taiwan, 2Division of Colorectal Surgery, China Medical University Hospital, Taichung, Taiwan, 3Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan, 4National Center for High Performance Computing, National Applied Research Laboratories, Hsinchu, Taiwan, 5Dianthus Maternal Fetal Medicine Clinic, Taipei, Taiwan. Trisomy 12q can be characterized by a clinically recognizable syndrome including craniofacial dysmorphy, growth failure, occasional brain malformations, abnormalities of the extremities, skeletal and thoracic malformations, cardiovascular defects, anogenital abnormalities like cryptorchidism, psychomotor delay and ontellectual disability The microarray assay exhibited an approximately 19.35Mb gain of the long arm of chromosome 12 at 12q24.21q24.33 (Fig. Polyakov: None. P09.003.D Transcriptomic characterization of 7q11.23 patient-specific induced pluripotent stem cells (iPSCs) and derivates Mar Costa-Roger 1, Bernd Kuebler2, Marina Alvarez-Estape1, Raquel Flores1, Luis Alberto Pérez-Jurado1,3, Ivon Cuscó1,4, Roser Corominas1,5 1Genetics Unit, Departament de Ciències Experimentals i de la Salut, Pompeu Fabra University, Hospital del Mar Research Institute (IMIM), Parc de Salut Mar and Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Barcelona, Spain, 2Regenerative Medicine Programme, Institut d'Investigació Biomèdica de Bellvitge, IDIBELL, L'Hospital de Llobregat, and Spanish National Stem Cell Bank-Barcelona Node, Instituto de Salud Carlos III (ISCIII), Madrid, Spain, 3Genetics Service, Parc de Salut Mar, Barcelona, Spain, 4Department of Clinical and Molecular Genetics and Medicine Genetics Group, VHIR, University Hospital Vall d'Hebron, Barcelona, Spain, 5Department of Genetics, Microbiology and Statistics, Barcelona University, Barcelona, Spain. Thevenon: None. Peng: None. Results: Using RNA-Seq we revealed 257, 100, and 228 DEGs with cut-off>1.5 and padj G and c.5457+81T>A in TRIP11 were present in homozygous state in all affected foetuses and the parents were heterozygous carriers. We further explore probabilistic relationships between nuclear genes associated with particular groups of mitochondrial variants, using Bayesian Networks. Published cases show lower mutation ratio in muscles than in blood, consistent with a genetic normalization, a selective pressure against mutant muscle cells. Jimoh: None. Martinez-Lopez: None. Until recently treatments have been limited but development of new therapeutics has highlighted the need to provide accurate and timely diagnosis. Capdevilla: None. Barner: A. P11.021.C Refinement of the 22q11 duplicated phenocritical locus in bladder exstrophy epispadias complex Glenda Maria Beaman 1,2, William G. 70.27% (1865/2654 associations), P = 6.9E−10; the most pronounced differences were related to anthropometric measurements (P = 1.4E−10). Nascimento: None. Conclusions: Observations of similar chromosome region deletions in patients from different populations from West Europe and the North Caucasus indicate that Xq21 region with its multiple conserved noncoding sequences is a hot spot for chromosome breaks. P12.138.B Evaluation of Plasma Cell Molecular Cytogenetic Findings of Myeloma Patients: One-Year Single-Center ExperienceIbrahim Kaplan, Hande Nur Cesur Baltaci, Sule Altiner, Sadiye Ekinci, Nedime Arzu Vicdan, Halil Gürhan Karabulut, Timur Tuncali, Hatice Ilgin Ruhi, Nüket Yürür Kutlay Department of Medical Genetics, School of Medicine, Ankara University, Ankara, Turkey. The molecular pathophysiology caused by heterozygous HRAS gain-of-function mutations have been analyzed in various tissues and cell types. The continuation of this study will be directed toward exploring the clinical advantage of the greater sensitivity offered by ddPCR, and the assessment how to best place ddPCR in the management of patients without an optimal response. Results: Sweat test (Nanoduct) was performed - conductivity 83mmol/l. It is often associated with hearing loss, hyperacusis or Meniere disease (MD). After genetic counselling the parents chose to continue their pregnancy and at this moment the pregnancy is continuing. To date, only postnatal descriptions have been described.The index was a male fetus with prenatally diagnosed micro- and brachycephaly, brain malformations and microretrognathia at 13th gestational week. Globally, more complex genomic profiles were identified in the CK group. The main clinical symptoms of disease were early onset of the disease at the age of 3-4 years, impaired coordination, frequent falls, regression of psychomotor development, seizures, subatrophy of the optic nerves. Most individuals with protein-truncating variants in KMT2E gene appear to present with generally mild developmental delay and intellectual disability, while patients with missense variants presented with the most severe phenotype. Approximately, 70% of ID cases are due to genetic factors, among those de novo pathogenic variants in dominant genes account for the majority of cases. Medical records including family history were evaluated. Rapid and accurate clinical analysis of variants from Whole Genome Sequencing assays using a user friendly web application Joseph Halstead All Wales Medical Genomics Service, Cardiff, United Kingdom. Genome sequencing resulted in a shortlist of three candidate genes with potentially pathogenic biallelic variants: TKT, P4HTM and USP4. Introduction: Axenfelt-Rieger syndrome (ARS) is an autosomal dominant genetic disorder characterised by ocular anterior segment disorders with systemic involvement. At the same time, the development of pancreatic diseases has no association with the genders (P = 0.1283). Poel: None. The neurofibromatosis give rise to a greater tumor burden for the nervous system than any other neoplastic disease. Altemaimi 1, Khadijah Ateyah1, Mohammad Dashti2, Raed Alroughani3 1Kuwait University, Jabriya, Kuwait, 2Dasman DIabetes Institute, Sharq, Kuwait, 3Amiri Hospital, Kuwait City, Kuwait. Materials and methods: The study included 17 patients with CML. When this occurs, the germline change shows lower pathogenicity prediction values that the somatic change. Dieterich: None. Therefore, our report solidifies the BICRA-based NDD as a distinct disease entity. Laffargue: None. Sousa CHULN - Hospital de Santa Maria, Lisbon, Portugal. Functional analysis of the mutational impact on immunocompetent cells is essential to understand the pathophysiology of NBAS disorders. Brain MRI demonstrated frontal bilateral and symmetrical lissencephaly and pachygyria, parieto-occipital polymicrogyria, subcortical heterotopia and hypoplasia of the cerebellar vermis. Damásio: None. P15.043.C Enzymatic DNA Synthesis (EDS) enables decentralized and same-day access to DNA oligos critical for the study and detection of SARS-CoV-2 Benoit Derrien 1, Chew Yee Ngan2, Rahul Maurya2, Sophie Romero1, Nadège Tardieu1, Henri Lachaize1, Maëllys Kevin1, Maryke Appel1, Margarita L. Tobias5, Laura Pölsler6,7, Yvonne Arens8, Jonathan Berg1, European Certificate in Medical Genetics and Genomics (ECMGG) Exam Committee 1University of Dundee, Dundee, United Kingdom, 2Heidelberg University, Heidelberg, Germany, 3University of Exeter Medical School, Exeter, United Kingdom, 4University of Zaragoza Medical School, Zaragoza, Spain, 5University of Glasgow, Glasgow, United Kingdom, 6Vrije Universiteit Brussel, Brussels, Belgium, 7Medical University Innsbruck, Innsbruck, Austria, 8Maastricht University Medical Centre, Maastricht, Netherlands. Many patients with low-GGT-cholestasis remain genetically undiagnosed. Here, we report the first time 47,XXY[83]/46,XX[4]/46,XY[13] mosaic Klinefelter syndrome with the MCTD. Results: Pomegranate extract (2.4%) reduces the levels of IL1b gene transcription by 16 times relative to control. Materials and Methods: we applied a CGP approach for mutational screening, Tumor Mutation Burden calculation, Microsatellite Instability and to identify RNA rearrangments, RNA rearrangements detection. P13.018.C Case report of two Brazilian families with Li-Fraumeni Syndrome phenotype with a variant of uncertain significance in TP53 Deivid C. Results: The patient showed the following clinical conditions: developmental delay, epileptic seizures, frequent convulsions, as well several dysmorhological features (macrocephaly, dolichocephaly, antimongoloid slanted eyes and micrognathia).The karyotyping demonstrated 47,XXX result, which did not correspond to the phenotype. Conclusion: Results from this survey provide a comprehensive diagnosis and clinical management overview for patients with NS across Europe. Introduction: When a chromosomal abnormality is identified prenatally, parents are faced with the option to terminate the pregnancy. We describe a patient with this variant and fatal outcome (she died from complications of cardiovascular surgery). Kristiansen: None. Kozlova2, Elena V. Hematological parameters of 89 low and 79 high altitude Tibetans were evaluated by automated hematology analyzer and manual methods. Funding: Research funded by PTDC/BTM-TEC/30164/2017 project; SL supported by 2020.05773.BD-FCT. Netea: None. Variants of uncertain significant (VOUS) were identified in two other families, including a heterozygous nonsense variant in the PELI2 gene, encoding an interleukin-1 receptor-associated kinase (IRAK)-interacting proteins, in three affected members from the same family and a de novo heterozygous 1.5 Mb deletion of 12p12.1p11.22 in a patient with enchondroma and type E brachydactyly. No expression of MAPKAPK5 protein isoforms and reduced levels of the MAPKAPK5-interacting protein ERK3 were detectable in patient derived cells. We identified 27 miRNAs hits with opposite expression profile to genes involved in immune response in bladder cancer, and 24 miRNAs hits with similar expression profile. 368 healthy Northern Ossetian individuals, including 248 Ironians and 65 Digorians, were analyzed for variants c. Introduction: Activating pathogenic variants of MET gene were identified in papillary renal cell carcinoma type 1 (PRCC1) with characteristic bilateral and multifocal PRCC1 tumors. DSTYK has been associated with autosomal dominant congenital anomalies of the kidney and urinary tract and with autosomal-recessive hereditary spastic paraplegia. Kásler: None. The clinical phenotype is extremely heterogeneous with ear anomalies, hemifacial microsomia, ocular defects, and vertebral malformations being the main features. Patients and methods: We present clinical evaluations of 3 patients with the clinical features of XGS, aged from 5 to 10 years. Genetic testing contributes to early diagnosis and targeted prevention of these cancers. A 17-year-old Caucasian male patient with sporadic exudative vitreoretinopathy/Coats' disease underwent complete ophthalmological examination, whole exome sequencing by NGS method was implied for searching causative genetic variants of the phenotype. Miliou: None. Parents were consanguineous (second cousins). K.C. Perumal: None. Although partial X duplication, the patient had no genital ambiguity or psychomotor disabilities until 7 months of age. Bene: None. Arruga: None. Results: The mutant "T" allele for SNP rs7969300 was detected in 17 out of 427 individuals, for a frequency of 0.0398. She had a normal course until the age of 6 years. A microhomology of 5 pb (TTATA) was found in both sides. Methods: We report a 41-year-old woman with a prior clinical diagnosis of Marfan syndrome (systemic score 8 and aortic root dilatation Z score 2.99). Plaiasu: None. alset: None. All tested patients showed increased inflammatory molecules compared to controls. The results confirm the late diagnosis of de novo achondroplasia during pregnancy, leading to major psychological and ethical issues for the parents. D.B. Everman: None. While giving genetic counseling, parents should be informed about the rate at which their next child becomes patient. Conclusions: NGS approaches can significantly improve diagnostics of rare genetic disorders. Wu: None. Gene ontology and pathway analyses suggested that the molecular mechanisms underlying syndromic OC were distinct from those in non-syndromic OC. We aimed to investigate the role of interaction between ETV5 and CXCL12 genes in humans with SCO syndrome. Serrano Mira: None. In all patients both drugs have been withdrawn and effectively replaced with Duloxetine in monotherapy; the subsquent clinical workup led to the diagnosis of LQTS in all four patients. Of those, 74.5% were identified in patients with a referral for suspicion of Hereditary Breast and Ovarian Cancer syndrome (HBOC). P18.043.A Polygenic Risk Prediction Ability of Gender-stratified Coronary Heart Disease Bahar Sedaghati-khayat 1, Maxime Bos2, Jingyi Tan3, Joyce B.J. van Meurs1,2, Andre Uitterlinden1,2, Catherine Hajek4, Jerome I. This ratio emphasize the importance of prenatal diagnosis. E.H. Steffensen: None. Dep Bioch Molec Genet. B.B.A. de Vries: None. Van Goethem: None. J.J. Cruz-Hernández: None. Metspalu: None. The aims of this study are 1) to clarify whether ART or maternal ages facilitates development of epimutation-mediated IDs (epi-IDs), and 2) to identify the differentially methylated region (DMR) that is vulnerable to the effect of ART and parental ages. It may be possible to develop these explorations of patient deliberation between clinical appointments to inform discussion within clinical appointments.ESRC Grant ES/R003092/1 L.M. Ballard: None. For the majority of affected individuals, the genetic cause remains elusive. Both the c.587A>G; p.(Asp196Gly) and the c.362dupC; p.(Glu122Argfs*7) variant cause absence of FKBP22 protein. Amyloid rate of change: absolute change divided by interval. Results: In 578 patients 9.7% (n = 56) PGVs in CPS-related genes were identified. J.M. Vázquez-Rodríguez: None. Gimeno Blanes: None. Kas: None. Results: The cascade familial screening and control re-sequencing were provided for proband with identified genetic variant p.S216L (g.38655290G>A, NM_198056.2:c.647C>T, rs41276525) in the canonical exon 6 of the SCN5A gene after receiving data from another laboratory. At each SNP, we eventually coded each individual genotype as the number of alleles falling into a high-confidence (>99%) archaic tracts and tested that SNP for association with phenotypes. Ms: None. Grange syndrome (GRNG - MIM#135580) is a rare recessive disorder associating variable features including diffuse vascular stenoses, brachysyndactyly and osteopenia with increased bone fragility. van der Helm, Robert M. Five additional cases were carriers for only one expanded pathogenic allele. P06.023.D Terezia Valkovicova 1, Zuzana Dobiasova1, Juraj Stanik2,1, Martina Skopkova1, Daniela Gasperikova1 1Slovak Academy of Sciences, Bratislava, Slovakia, 22nd Department of Pediatrics, National Institute of Children's Diseases and Faculty of Medicine, Comenius University, Bratislava, Slovakia. However, the full range of pathogenic variants, leading to the development of HCM, has not yet been described. G.S. Bhavani: None.

Background: Parental lineage has been shown to increase the risk of Alzheimer's disease (AD) in the offspring, with greater risk attributed to maternal lineage. Lunnon: None. (2020) have developed a 5-factor model that captures transdiagnostic symptom dimensions in these disorders. The maternal grandmother suffered from a mild form of axillary HS. Calvert: None. FKBP5 mRNA levels decrease after antipsychotic treatment (**p = 0.0095). Engaging enough patients to implement these initiatives can be difficult. Our objective was to examine the detection rate of clinically significant chromosomal microarray analysis (CMA) findings in pregnancies with CFMs. Methods: Data from all CMA tests in pregnancies with sonographic diagnosis of CFMs (cleft lip and/or palate, malformations of eyes, nose or ears, micro-retrognathia etc) performed between January 2016 and April 2020 were retrospectively obtained from the Israeli Ministry of Health computerized database. Maré: None. Lubout, Hessel P. van Meurs: None. Ownership Interest (stock, stock options, patent or other intellectual property); Significant; GenDx. P15.025.A Estimating the X chromosome-mediated risk for developing Alzheimer's disease Carmel Armon, Sharon Wolfson, Rivka Margalit, Liraz Avraham, Yael Bugen, Amir Cohen, Adi Meiri, Ran Shorer Tel Aviv University School of Medicine and Shamir (Assaf Harofeh) Medical Center, Zeriffin, Israel. Kirk1, Terri P. Downstream analysis of chosen modules followed. Trio whole exome sequencing of the proband and her parents confirmed the MECP2 variant but did not identify any additional pathogenic variants in other genes. Clinically, the various disorders manifest themselves through repeated trauma and mutilation. R. Jares: None. Brioude: None. The rs657152 A-allele was observed with the highest frequency in the populations of Burzyan Bashkirs (53.12%) and Kazakhs (47.5%), while the lowest frequency was shown in Evens (33.3%). Brás2, Rita Quental4, Miguel Leão4, Joana Damásio1,5, Marina Magalhães5, João P. Abdelmoula: None. Results: Based on the filtering and variant prioritization strategies mentioned above, 24 candidate CRC-predisposing genes were selected. Jödicke: None. Ahmed1, Muntaser E. Kirsch: None. Hallmark: A. Results: The automated method performed equivalently to manually performed assays, as 1 ng RNA input produced cycle threshold (CT) values of 21.60 ± 0.06 and 21.68 ± 0.08 for manual and automated methods, respectively. With increased scalability and usability, this analysis can now be easily performed on a wide range of cfDNA samples. Silveira-Santos: None. However, the interpretation of the pathogenicity of rare missense variants in the absence of previous reports or a functional assay is challenging. In contrast to women, we found that men have enriched heritabilities across most phenotypes on the X chromosome. Costa: A. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Modest; Canada First Research Excellence Fund, Healthy Brains for Healthy Lives. Eight females and nine males were asymptomatic carriers of a CELSR1 variant. Piekutowska-Abramczuk: None. Tosi: None. Caroli: None. It also offers title protection to legally recognized professionals. 6 patients who have GSD preliminary diagnosis but CES made the clear definitive diagnosis as different: In 4 cases has SNV, remain 2 has homozygous exonic deletions on FBP1and LPIN1 genes. In total, we identified 12 single variants in 12 patients which one of them is a known copy number variation (CNV) reported for hearing impairment. Methods: Whole-exome sequencing data from unresolved gastric cancer cases (n = 83) was processed by the RD-Connect Genome-Phenome Analysis Platform and annotated using the Ensembl Variant Effect Predictor algorithm. de Voer2, Nicoline Hoogerbrugge*2, Stefan Aretz*1,9, * contributed equally 1Institute of Human Genetics, Medical Faculty, University of Bonn, Bonn, Germany, 2Department of Human Genetics, Radboud university medical center, Radboud Institute for Molecular Life Sciences, Nijmegen, Netherlands, 3Instituto de Investigação e Inovação em Saúde (i3S), Universidade do Porto, Porto, Portugal, 4Institute of Molecular Pathology and Immunology of the University of Porto (IPATIMUP), Porto, Portugal, 5Faculty of Medicine, University of Porto (FMUP), Porto, Portugal, 6MGZ - Medizinisch Genetisches Zentrum, Munich, Germany Arbeitsgruppe erbliche gastrointestinale Tumore, Medizinische Klinik und Poliklinik, Munich, Germany, 7Campus Innenstadt, Klinikum der Universität München, Munich, Germany, 8Hereditary Cancer Program, Catalan Institute of Oncology, IDIBELL and CIBERONC, Barcelona, Spain, 9National Center for Hereditary Tumor Syndromes, University Hospital Bonn, Bonn, Germany. The molecular evaluation was firstly performed on tissue samples using the 14-genes NGS panel HBOC (Devyser). Focused on the genes involved in Wnt signaling, we identified 44 rare, predicted damaging variants in 34 Wnt-related genes. Among the genetic modifiers identified in DMD patients, THBS1 has higher network topological parameters. These disorders most often involve trinucleotide repeats but have been associated with other types of repeat arrays. Hoffmann, Roche, Sanofi aventis, Bayer. Galibert: None. Genetic analysis of the tumor biopsy was performed by conventional cytogenetic analysis, HR-CGH and FISH. Therefore, updates of these tools are reflected in MobiDetails results and regular visits to key variant pages can bring new insights and help refine classification. Dragomir: None. Zurek: None. F.B. Cristian: None. Although more information is still needed to understand these mechanisms, our results suggest that in heterozygous animals TBCK functions are affected and this can have further effects in metabolism and behavior. O.M. Drapkina: None. Results: We report the first cohort of patients with BRD4-related Cornelia de Lange-like syndrome and describe new cardinal clinical findings. Results: A de novo heterozygous likely pathogenic (Class 4) variant c.3557C>T p.(Ala1186Val) in FLNC was found in both patients, while additional pathogenic variants were not detected. Sadowski: None. El Chehadeh: None. L.V. Hanna: None. Its deficiency leads to uncontrolled activation of the kinin-kallikrein system resulting in an extended generation of bradykinin. Gene Ontology (GO) analysis and pathway enrichment analysis was performed to investigate relationship between miRNA and targeted mRNA. The underlying molecular abnormality, a duplication of the entire OVOL2 gene, suggests a gene dosage effect. Manickam: None. Mekke: None. Over 75% of patients analyzed were OOC. M.S. Hassan: None. Background: Genetic and/or non-genetic causes of serrated polyposis syndrome (SPS) are widely unknown. P23.030.B New British Society for Genetic Medicine (BSGM): Ethical issues relating to prenatal genetic testing Adeline Perrot, Ruth Horn Ethox Centre, Oxford, United Kingdom. Two patients had heterozygous microdeletions in chromosome 22q11.2. Abnormal lymphocyte proliferation, hypogammaglobulinemia, and autoimmune hemolytic anemia observed in both patients seem accountable to 22q11.2 microdeletion. Tucker: None. Radzhabov2,3, Vadim A. Similarly, genetic differences between an Afro-descendant population (Magüí Payán) and mestizo populations (Pasto and Policarpa) may be the result of historical processes or natural selection. Forstner1,10,11 1Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Bonn, Germany, 2Department of Psychiatry and Psychotherapy, University of Marburg, Marburg, Germany, 3Center for Mind, Brain and Behavior, University of Marburg, Marburg, Germany, 4Department of Neurology, Klinikum rechts der Isar, School of Medicine, Technical University of Munich, Munich, Germany, 5Department of Psychiatry and Psychotherapy, University of Münster, Münster, Germany, 6Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany, 7Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Munich, Germany, 8Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany, 9Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, Germany, 10Institute of Neuroscience and Medicine (INM-1), Research Center Jülich, Jülich, Germany, 11Centre for Human Genetics, University of Marburg, Marburg, Germany. Douet: None. Besides gastro-oesophageal reflux there were no general health problems. Ghorani: None. Tamm: None. Gomez-Peregrina: None. The association of LoF variants with complex diseases and traits may lead to the discovery and validation of novel therapeutic targets. Questions covered pharmacogenomic knowledge, life-threatening ADRs (specific to SJS (abacavir and HLA-B*57:01; carbamazepine and HLA-B*15:02)), and perspectives on pharmacogenomic implementation barriers. Baerlocher: A. We aimed to present the deletions in the 13q region of our patient and their clinical implications in our case. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Modest; National Health Association, South-Eastern Regional Health Authority. Funding: MRC (NNF17SA0031406), TOK (NNF20OC0063707), DB (NNF17CC0026760) M.R. Christiansen: None. Minguet: None. Black1, Jamie M. Conclusion: Our studies may well confirm that XRCC1-Arg399Gln and XPG-Asp1104His polymorphisms may influence the reproductive risk factors and increased risk of BC in Tanzania. Introduction: Data infrastructures are being developed to enhance and facilitate the sharing of cohort data internationally. In addition, comparing acceptance before and after dialogue signals the potential impact of participation. The risks were higher in specific populations. The COL1A1 rs1107946 TT genotype was significantly over-represented in the MSST injuries (case) group (11%) when compared to the CON group (3%, p = 0.042). Gomes: None. We carried out several workshops "Application of Artificial Intelligence in the Diagnosis of RDs" together with FDNA for doctors and medical students. Stradomska: None. Results: The participants' answers were: PGS is useful regardless of family history (92%), it would help to avoid stress of having a sick baby (48%), PGS increases the chances of having a healthy baby (45%), carriage identification can change relationship between partners (46%) and attitude towards oneself (34%). Annilo: None. Seferiadi: None. Also mtDNA copy number did not differ between PD patients and control subjects. Moreno-Martinez: None. Methods: In this poster, we evaluate the automation of the AmpliSeq for Illumina Cancer HotSpot Panel v2 protocol on the new Biomek NGeniuS. S.E. McKeown: None. Students could connect remotely and carry out their analysis without installing anything on their own device. Mullegama15, Houda Zghal Elloumi15, Adi Reich15, Samantha A. Second harmonic generation florescence microscopy revealed HET bones contain mostly disordered matrix(p 90% of cases1) and variants in APOB, PCSK9 and LDLRAP1 (10% of cases). GraphPad Prism was used for statistical analysis. It was therefore possible to reveal an Xp duplication but without detection of a distal 16q monosomy. This study focused on participants' sociodemographic background, reproductive history, genetic conditions, number of children (healthy/affected), number of IVF cycles, attendance at genetic counselling sessions, donation of hematopoietic stem cells, attitudes towards associated moral issues, embryo cryopreservation and prenatal diagnosis (PND) after PGT. Schmidt9, Peppi Koivunen* contributed equally4,5, Johanna Uusimaa* contributed equally2,4,6 1Department of Clinical Genetics, Oulu University Hospital, Oulu, Finland, 2PEDEGO Research Unit and Medical Research Centre Oulu, University of Oulu and Oulu University Hospital, Oulu, Finland, 3Institute of Biomedicine, University of Turku, Turku, Finland, 4Biocenter Oulu, University of Oulu, Oulu, Finland, 5Faculty of Biochemistry and Molecular Medicine, Oulu Centre for Cell-Matrix Research, University of Oulu, Oulu, Finland, 6Department of Children and Adolescents, Division of Paediatric Neurology, Oulu University Hospital, Oulu, Finland, 7Kaiser Franz Josef Hospital with G.v. Preyer Children's Hospital, Department of Pediatrics, Vienna, Austria, 8Department of Clinical Genetics, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands, 9Neuromuscular Research Department, Medical University of Vienna, Centre for Anatomy and Cell Biology, Vienna, Austria, 10Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki, Finland, Helsinki, Finland, 11Psychiatric & Neurodevelopmental Genetics Unit, Massachusetts General Hospital, Boston, MA, USA, 12The Stanley Center for Psychiatric Research, The Broad Institute of MIT and Harvard, Cambridge, MA, USA, 13Texas Children's Hospital, Houston, TX, USA, 14Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA, 15Northern Finland Laboratory Centre NordLab and Medical Research Centre, Oulu University Hospital and University of Oulu, Oulu, Finland, 16Department of Pathology, Oulu University Hospital, Oulu, Finland, 17Department of Medical Genetics, Genome-Scale Biology Research Program, University of Helsinki and Haartman Institute, Helsinki, Finland, 18Baylor Genetics, Houston, TX, USA. McKnight: A. Discussion: This project utilises high-quality WGS data and gold-standard PCR data. Results: This mutation leads to truncation of the entire cytosolic C-tail of GluN2B subunits. Previously described cases of B3GAT3-deficiency were all children with phenotypes ranging from prenatal manifestation and early lethality to less severe. Eye problems (most commonly divergent squint and/or proptosis) were seen in five patients. Methods: As proof of principle, twelve pediatric B-cell precursor ALL samples from ALL-BFM-2000 and AIEOP-BFM-ALL-2017 were analyzed by means of OGM using the Saphyr system (Bionano Genomics). The isolates carrying the blaCTX-M-15 gene were ascribed to phylogroups B2 and D, and the blaCTX-M-1-carrying isolate was typed as phylogroup C. YIF1B is an essential protein involved in the anterograde trafficking from the endoplasmic reticulum to the cell membrane, and in Golgi apparatus architecture. karić-Jurić: None. Mezher: None. In both periods, the couples with reproductive problems preferred face-to-face disclosure, in contrast with the pregnant women's group with statistical significance. Here we investigate the population transcriptomics in a preeclampsia (PE) model using WGCNA. Introduction: The human brain is a highly sophisticated and complex organ, yet to be completely understood. Tabet: None. S.A. Savage: None. Mourmoura: None. A mild association was found between INV.S and wHRS (P = 0.049), with individuals with a higher wHRS showing a lower diversity. Bekri: None. Swarovskaya: None. Leone: None. Di Sarno: None. Results: The legal regime of the biobank as a complex object consists of the regimes of biomaterials and information collected on their basis specified in the law. Dysmorphic features were rather subtle and non-specific and therefore not considered as a recognizable facial gestalt. Two SNPs, rs1132787 (GYPA) and rs522521 (LOC105371557) were associated with diabetic neuropathy, while seven (one shared with diabetic neuropathy) rs2477088 (PDE4DIP), rs522521 (LOC105371557), rs4852954 (NAT8), rs6032 (F5), rs6935464 (RPS6KA2), rs7236163 (ZNF519), and rs3095447 (CCDC146) (latter is also shared with ophthalmic complications) were showed significant association with macrovascular complications. This observation highlights the efficiency of our whole-gene approach to detect intronic structural variants and solve unexplained haemophilia B. CDC25B (Cell Division Cycle 25B), a member of the CDC25 family of phosphatases, is a tyrosine protein phosphatase, which induces the mitotic progression and activates the cyclin dependent kinase CDC2 by removing two phosphate groups. Mosaicism affected the germline in one patient, being his daughter a heterozygous carrier of the same variant. P09.128.A Identification of enhancer regions to expose novel genetic causes of spinocerebellar ataxia Fatemeh Ghorbani, Eddy N. Results: In studied patient variant c.5637_5638insA (p.Leu1880ThrfsTer6) in TANGO1 gene was detected. The mutation of TCIRG1 was found (G 2415A). Subías: None. Patients' variables included TKI treatment (imatinib and/or nilotinib), OS, cytogenetic (CCyR) and molecular responses (MMR, MR4, and MR5). We also reviewed the data of the 21 initially described and the 5 recently reported patients with SIDDT. All the types have molecular confirmation except the hEDS, but we found some genes (TNXB,ELN,PIEZO2) that could be implicated, requiring future studies. Halford: None. Tenaiji21, Shahnaz Ibrahim22, Fatima Khan22, Henry Houlden23, Vijayalakshmi S. Buonadonna: None. Á. Individuals with two different HBOC tumors (OR = 6.29, p C (p.Glu2904Gln) was not found in the population databases. Pregnancy and birth were uneventful; growth and psychomotor development were normal. The main categories and pathways in these clusters are processes of the cytokine signaling (FDR = 0,005). Patient 1 presented with speech delay, autism, frequent headaches, balance problems, muscular hypotonia, mild proximal and facial muscle weakness, dysarthria, fatigue, scoliosis, connective tissue weakness, joint hypermobility, juvenile idiopathic arthritis, osteoporosis with compression fractures, arterial hypertension, and obesity. BouChedid: None. Conclusions: The unfavorable effect of combined BRCA1 and p53 gene variants with aggressive course and resistance to treatment in patients with breast cancer was defined. Results: Following 5' leader end of CD8A mRNA, is attached nucleotide coding for a modified human TFIIIA polypeptide (TI9606) designed to target the poly uracil tail of negative-sense coronavirus's genome. Conclusions: The phenotypic abnormalities in distinct KTCN CE regions are related to the identified transcriptomic alterations. Material and methods: We analyzed 205 patients with suspected IMD using Whole Exome sequencing (WES). From these, we developed PredWES: a statistical model predicting the probability of a positive WES result solely based on the phenotype of a patient. Flisar: None. Wortmann: None. Simao: None. J.R. Perkins: None. This CAG repeat is somatically unstable in a process that is CAG length-, tissue- and age-specific in HD full-penetrance (n ≥ 40) alleles. Martínez-Gil: None. Conclusion: Genetic screening revealed variants with likely functional effects at high rates, in 63% and 35% of the SCD cases with non-diagnostic and diagnostic cardiac abnormalities, respectively. As in only 5-20% of the patients pathogenic variants are found in currently known PID genes, we hypothesize that defects in additional DNA damage response genes may be involved in PID patients prone to malignancies. We present a case of patient with the previously described PACS2 c.624G>A; p.Glu209Lys variant. Coppedè: None. Evangelisti: None. Support: LifeMap Sciences grant R. Piulats5, Ettore D. Introduction: Individuals carrying pathogenic/likely pathogenic variants in the BRCA1/2 genes have a high lifetime risk of developing breast and ovarian cancer. Zamba-Papanicolaou: None. Vasilyeva, Rena A. In addition, we address key challenges that arise in real data: missing trait measurements and related individuals. These genetic variants were prevalidated with Integrative Genomics Viewer (IGV). Daou: None. Background: (Epi)genetic disorders associated with small-for-gestational-age with short stature (SGA-SS) include imprinting disturbance (IDs). Westphal: None. Ostergaard: None. Sleutjes: None. Our data suggest that miR-29b inhibition act on multiple mechanisms that regulated cell fate, and therefore may serve as a therapeutic target in TNBC. It has been estimated that about 0.3% of all variations are due to de novo insertions. Harmat: None. Kapahi: None. We evaluated microdeletions of the Y-chromosome STS markers AZFa, AZFb and AZFc, ZFX/ZFY, terminal sY160 regions by using DNA Fragment analysis. Buchi: None. P01.074.B Pregnancy loss and Exome sequencing analysis (WES) Aicha Boughalem 1, Detlef TROST1, Constance Wells2, Audrey Lamouroux2, Viorica Ciorna-Monferrato3, Amandine Diakiese4, Pascale Kleinfinger4, Laurence Lohmann4, Armelle Luscan4, Mylene Valduga4, Jean-Marc Costa1, Patricia Blanchet2 1Laboratoire CERBA, Saint Ouen l'Aumône, France, 2Département de Génétique Médicale, Centre de Référence « Anomalies du Développement et Syndromes Malformatifs », CHU Hôpital Arnaud de Villeneuve, Montpellier, France, 3Génétique Médicale et Oncogénétique, Hôpital Femme Mère Enfant, Metz-Thionville, France, 4CERBA, Saint Ouen l'Aumône, France. After birth of the second sibling, due to the different clinical features not consistent with phenotypic heterogeneity of a KATNB1-related syndrome in the same family, we performed Trio Whole Exome Sequencing (WES). P08.005.C Inherited ARID1B variants: evidence of non-pathogenicity or variable expression? Unfavorable alleles of various genes have a relatively small influence on the disease risk when they appear individually, but in combination, they predispose an individual to RA development. CONCLUSIONS: Genetic evaluation (testing and counseling) is recommended in each patient with isolated or syndromic LVNC. Materials and Methods: A male, 14 years of age, was referred for genetic assessment for intellectual disability and abnormality of cerebral cortex. The MLH1 variant c.1558+1G>A showed a splicing defect apparent as partial retention of intron 13 in 20% of the transcripts. Five new genes (SPTBN1, CCDC87, KCTD10, MYO1H, MMAB) were prioritized for functional follow-up. van der Werf: None. Their parents both had consanguineous marriages. DYNC1H1 (MIM#600112) gene encodes a heavy chain 1 of the cytoplasmic dynein. P20.003.B Resistance profile and genetic diversity among selected ESBL-producing Escherichia coli isolates from urocultures in a portuguese hospital Isabel Carvalho 1,2,3,4,5, José António António Carvalho6, Ana Paula Castro6, Sandra Martínez-Álvarez5, Gilberto Igrejas2,3,4, Carmen Torres5, Patrícia Poeta1,4 1Microbiology and Antibiotic Resistance Team (MicroART), Department of Veterinary Sciences, University of Trás-os-Montes and Alto-Douro), Vila Real, Portugal, 2Department of Genetics and Biotechnology, UTAD, Vila Real, Portugal, 3Functional Genomics and Proteomics Unit, UTAD, Vila Real, Portugal, 4Laboratory Associated for Green Chemistry (LAQV-REQUIMTE), New University of Lisbon, Monte da Caparica, Portugal, 5Area Biochemistry and Molecular Biology, University of La Rioja, Logroño, Spain, 6Medical Center of Trás-os-Montes e Alto Douro E.P.E., Vila Real, Portugal. The identification of disease-associated variants provided information for follow-up genetic counseling of recurrence risk and management of subsequent pregnancies. Routine high-throughput molecular testing in LCA yields 70%-80% of genetic diagnosis. Results: After variant filtering, 37 variants were described: 12 Pathogenic or Likely Pathogenic variants were identified in 6 different genes (5 in ATM, 2 in BRCA2, 2 in TP53 and one for BRCA1, FANCM and PALB2, each). Different genetic models could explain ASD, ranging from monogenic disorder or copy number variation to polygenic disease. Smith: None. Posar: None. Grinberg: None. Accordingly, we have found decreased levels of CIII and accumulation of CIII-specific subassemblies devoid of UQCRC1, UQCRC2, and UQCRFS1 subunits in the patient's fibroblasts. Soritau: None. (Asp855Glu). B.A. Chioza: None. Due to the clinical variability of the disease, diagnosis can be difficult; with misdiagnosis also a possibility. Anikster: None. In the second patient, FluiDMD analysis showed lack of DMD transcript spanning exon 1-53, with the sole Dp71 isoform expressed. Three patients carried pathogenic variants in Lynch Syndrome genes and four patients carried pathogenic variants in two genes. Clinical investigations and treatment of the patient was performed at the Dr. von Haunersches Childrens Hospital in Munich, Germany. The prevalence of lymphatic problems seem to differ between genes. Agolini: None. Employment (full or part-time); Significant; HUG, Geneva University Hospitals. Rocca: None. Conclusions: Rare variants in BLK, KLF11 and PAX4 do not cause MODY and should not be included in diagnostic testing for MODY. van den Heuvel-Eibrink1, Martha A. Furthermore, this approach increases the chance to make available genetic counseling, presymptomatic genetic testing, and gynecological cancer prophylaxis to female relatives who turn out to be healthy carriers of deleterious germline variants. This study was funded by the World Class Research grant (Ministry of Research and Technology/National Research and Innovation Agency, Indonesia Gunadi: None. Altin: None. Together these assays are cumbersome, low resolution, expensive, and require specialized, highly trained operators. MobiDetails annotations are dynamic, as they either rely on local files updated on a regular basis (e.g. ClinVar data) or on live API calls (e.g. to LOVD, LitVar for literature queries, Intervar or MetaDome). Syndromological diagnostics was performed using the diagnostic program "Face2gene"; suspected KMS; cytogenetic, molecular genetic research is recommended to verify the diagnosis. Results: We observed that SLC6A4 expression is upregulated in GTS individuals compared to controls. These alterations of TL may be a result of telomeric region recombination and, thus, does not require telomerase activity which is absent until the blastocyst stage. Traficante: None. To study this, we re-analyzed recently published single-cell expression data from the Mouse Organogenesis Cell Atlas (Cao et. Irigoyen: None. Venz: None. Del Fattore: None. That make them prominent clinical markers to predict a prognosis and choose the appropriate therapy. C.J. Dommering: None. T.T. Lindenberg: None. Sonigo: None. Introduction: Cystic Fibrosis (CF) is an autosomal recessive disease associated with mutations in CFTR. Methods: We identified previously-reported pathogenic rare variants in COL4A1, COL4A2, TREX1, CTSA and HTRA1 and their reported phenotypes, mapping phenotypes to hospital admission and primary care codes. She has peculiar stereotypical "dancing" movements with her hands (less with her feet). Around 25-50% of GDD cases can be secondary to genetic causes. Cormier daire: None. The expression of the transcripts in gastric cancer samples was determined and further analysis of their correlations currently in process. Over 200 common susceptibility variants have been identified. The heterozygous carrier frequency of mutations 4582_4583insT in CUL7 gene, c.5741G>A in NBAS gene, c.806C>T in DIA1 gene, c.1090G>C in FAH gene, c.-23+1G>A in GBJ2 gene causing five monogenic disorders prevalent among yakut ethnic group: 3-M syndrome, SOPH-syndrome, Tyrosinemia type 1, Methaemoglobinaemia type 1, Nonsyndromic hearing loss and deafness (DFNB1) type 1A respectively was estimated using low density DNA microarray. The prevalence of postnatal lymphatic disorders caused by pathogenic variants in RIT1 was 32.6%, caused by pathogenic variants in SOS1 44.4% and in pathogenic PTPN1 variants 16.5%. Alonso-Betanzos: None. Furthermore, we employed a prior-guided gene expression network inference strategy to analyze GR-regulated co-expression patterns within and across brain regions. We used sanger sequencing for mother and father carrier screenings. We analysed the burden of high constraint variants of each type in both genders comparing their allelic frequencies with Swedish controls from SWEGEN database. Spanish National Cancer Research Center (CNIO), Madrid, Spain, 6Department of Immunology and Oncology, National Center for Biotechnology (CNB-CSIC), Spanish National Research Council, Madrid, Spain. Yingchoncharoen: A. Target gene expression was analyzed by RT-PCR. Second family segregates two rare, predicted pathogenic variants NM_001134407.3 (GRIN2A):c.3505C>T, (p.R1169W) and NM_001010848.4 (NRG3):c.1951G>A,(p.E651K). Cerebral ultrasound was normal. Introduction: Kabuki Makeup Syndrome (KMS) OMIM 147920 is a rare genetic disease characterized by phenotypic traits, mental retardation, and autistic symptoms. This study aimed to evaluate the predictive performance of a 12-SNPs PRS in combination with already established PD-environmental/lifestyle factors. Consultant/Advisory Board; Modest; MyHeritage. As a sanity check we prove that the most suitable accessible tissue to investigate heart arrhythmias is skeletal muscle. Diebold: None. Liao: None. Siquier-Pernet: None. Variants in the 363 identified genes were extracted from ALS-specific and general genomics datasets, creating a final database of 1.5 million variants. BIGNON9,5, Jean CHIESA10, Thierry FREBOURG11,5, Sophie GIRAUD12,5, Sophie LEJEUNE13, Jean-Marc M. Wakeling1, Olivia Knox1, Kevin Colclough2, Caroline Wright1, Sian Ellard1, Andrew T. We also identified two unique sporadic TSC2 mutations in each of an angiomyolipoma and a facial angiofibroma, in a patient with minimal TSC clinical features. To confirm absence of the variant in the populations, we have genotyped population samples of European origin (N = 327) and of Asian origin (Tuvinians and Yakuts, N = 224) consisting of peoples living in Siberia. Vissers1 1Department of Human Genetics, Donders Institute for Brain, Cognition and Behaviour, Radboudumc, Nijmegen, Netherlands, 2Department of Human Genetics, Radboudumc, Nijmegen, Netherlands, 3CNAG-CRG, Centre for Genomic Regulation (CRG), The Barcelona Institute of Science and Technology, Barcelona, Spain, 4Department of Clinical Neurosciences, University of Cambridge, John Van Geest Cambridge Centre for Brain Repair, Cambridge, United Kingdom, 5Department of Laboratory Medicine, Translational Metabolic Laboratory, Radboudumc, Nijmegen, Netherlands, 6Department of Human Genetics, Radboud Institute for Health Sciences, Radboudumc, Nijmegen, Netherlands, 7Department of Internal Medicine, Radboudumc, Nijmegen, Netherlands, 8Department of Medical Imaging, Radboudumc, Nijmegen, Netherlands, 9Department of Human Genetics, Radboud Institute for Molecular Life Sciences, Radboudumc, Nijmegen, Netherlands, 10Laboratoire de Génétique Moléculaire, Service de Génétique Médicale, CHU Bordeaux – Hôpital Pellegrin, Bordeaux Cedex, France, 11Département de Génétique, APHP Robert DEBRE University Hospital and INSERM U1141, Paris, France. P02.065.B Genetic study of Italian families affected by small fibre neuropathy identified variants in predisposing pain phenotype Kaalindi Misra 1, Silvia Santoro1, Andrea Zauli1, Margherita Marchi2, Erika Salvi2, Raffaella Lombardi2, Daniele Cazzato2, Filippo Martinelli Boneschi3,4, Massimo Filippi5,6,7,8, Federica Esposito1,5, Giuseppe Pinter Lauria2,9 1Laboratory of Human Genetics of Neurological Disorders, IRCCS San Raffaele Scientific Institute, Milan, Italy, 2Neuroalgology Unit, Foundation IRCCS Carlo Besta Neurological Institute, Milan, Italy, 3Department of Biomedical Sciences for Health, University of Milan, Milan, Italy, 4Neurology Unit, Foundation IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy, 5Neurology and Neurorehabilitation Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy, 6Vita-Salute San Raffaele University, Milano, Italy, 7Neurophysiology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy, 8Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan, Italy, 9Department of Biomedical and Clinical Sciences "Luigi Sacco", University of Milan, Milan, Italy. The Elson neutrality test did not reveal any deviations from neutrality in the "highland"; in the "lowland" sample, the test revealed a deviation from neutrality for the MTND6 (p = 0.007) and MTCO2 (p = 0.02) genes. The identified variants were evaluated in molecular homology models generated with the Modeller 9.22 software and stability programs were used to predict ΔΔG caused by residue changes. Results and conclusion: We identified 59 alleles in 8 pharmacogenes (CYP2C9, CYP2C19, CYP3A5, CYP4F2, VCORC1, DPYD, TPMT and NUDT15). The aim of this study was to identify a de novo reciprocal translocation. Clowes: None. Röner: None. Mosiello19, S. This association was confirmed further in the multivariate logistic regression analysis taking into account several potential confounding factors (OR = 3.34 (1.01-11.00), p = 0.048). According to his physical examination and the results of the molecular analyses we have concluded that this novel variant causes Brittle cornea syndrome and genetic counseling was given to family. Introduction: Spinal Muscular Atrophy (SMA) is an autosomal recessive neuromuscular disorder due to homozygous loss of function in SMN1 gene. P18.044.B Idéfix: Identifying accidental sample mix-ups in biobanks using polygenic scores Robert Warmerdam 1, Pauline Lanting1, LifeLines Cohort Study, Patrick Deelen1,2, Lude H. Extracutaneous findings were noted in 17 (68%) cases; ocular manifestations (28%), neurological abnormalities (28%), hair abnormalities (20%), dental anomalies (12%), nail dystrophy (8%). W.J.Young is funded by the Medical Research Council (Grant code MR/R017468/1) W.J. Young: None. Conclusions: These cases illustrate the intra- and extra-familial spectrum of variability associated with VARS2 variants, including milder phenotypes that complicate genetic counselling, especially in the prenatal setting. Diagnostic variants were identified in 71 genes, with nearly half of these genes (n = 33, 46.5%) contributing uniquely to a molecular diagnosis for a single patient. Therefore, in this study we used our heterozygous mice model (tbck+/-) to test this hypothesis. Battistuzzi: None. E.G. Burchard *: None. Van Dijk: None. These observations led to an increased research interest in cfDNA for so-called liquid biopsies. Prior studies have shown two mtDNA poly-C tracts located in the non-coding region (16184-16189 and 303-315) are associated with diseases such as cancer. Fluent BioSciences has developed a novel scRNA-Seq approach with Pre-templated Instant partitions (PIPseq) that enables the analysis of thousands of cells without requiring complex instrumentation and consumables. It is to be expected that LOH is frequent in SPMs as well. The purpose of our study was to evaluate the impact of IL-6 (G174C, rs1800795) and VDR (TaqI or T1056C, rs731236; BsmI or G283A, rs1544410) genes variants on the course of severe COVID-19 pneumonia. Gjermeni: None. Işık: None. We screened for differential expression of neurotransmitter receptors and their genes in the cornu ammonis (CA) and dentate gyrus (DG), to gain insight into their regional specificity. Objectives: This study was aimed at investigating the association of the single nucleotide polymorphism of tumor necrosis factor receptor associated factor 6 (TRAF6), rs540386, with low bone mineral density (BMD) among patients with rheumatoid arthritis (RA). Introduction: Many severe genetic disorders cannot be identified prenatally by cytogenomic analyses and, often, the parents are unaware of their carrier status. Romão: None. P17.023.B DIVAs: a phenotype-based machine-learning model to assess the pathogenicity of digenic variant combinations Federica De Paoli 1, Ivan Limongelli2, Susanna Zucca2, Federica Baccalini1, Valentina Serpieri3,4, Fulvio d'Abrusco4, Marina Zarantonello5, Giovanna Fabio6, Maria Carrabba6, Enza Maria Valente3,4, Paolo Magni1 1Department of Electrical, Computer and Biomedical Engineering, University of Pavia, Pavia, Italy, 2enGenome srl, Pavia, Italy, 3IRCCS Fondazione Istituto Neurologico Nazionale Casimiro Mondino, Pavia, Italy, 4Department of Molecular Medicine, University of Pavia, Pavia, Italy, 5Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy, 6Internal Medicine Department, Primary Immunodeficiencies Centre, Fondazione IRCCS Ca' Granda Ospedale Maggiore, Milan, Italy. With numbers of GEs in this range, multiple informative SNPs need to be analysed to increase the power of detecting significant skewing of allele ratios in individuals with SPM compared to balanced ratios expected in healthy individuals. Consultant/Advisory Board; Modest; Biogen, EMD Serono, Genentech, Tilos Therapeutics, Inc, Everest Medicines Ltd, Magnolia Therapeutics, Tiziana Life Sciences, IM Therapeutics, MedDay Pharmaceuticals, vTv Therapeutics. Further detailed multidisciplinary studies will better elucidate 22q11.2 microdeletion syndrome. Most affected individuals have an autosomal dominant disorder caused by heterozygous variants in either of the type I collagen genes (COL1A1 or COL1A2). Consultant/Advisory Board; Modest; Novo Nordisk, FDNA. The discrepancy between sequencing data and SNP score may suggest still unknown regulatory regions located more far apart from LPA. Hopefully in the near future we will be able to understand the basis for these pathologies and to establish the connection that exists between heterozygosity in animals and the presence of a phenotype in humans. ESR1 gene expression is important for embryo implantation and pregnancy outcome, neuroprotection throughout life from antenatal period, and also has an organizational impact on the formation of long-term behavioral and cognitive functions, as well as maintaining energy homeostasis. Most of the genes identified are involved in the functioning of the heart in general and the sarcomere in particular. The allele that tags the O blood group at the ABO locus, was associated with higher estradiol levels. Because genetic counseling may greatly influence parental decisions, advocating the training of more genetic counselors is very important. Changes in the expression of the DNM2 gene in treated patients with PD suggest that this gene is may be involved in processes associated with dopamine agonist therapy. Chromosomal molecular analysis, performed after amniocentesis for multiple soft markers, was normal. P16.033.D Solving the unsolved: 4 years of experience of the Italian Telethon Undiagnosed Diseases Program Raffaele Castello 1, Annalaura Torella1,2, Manuela Morleo1, Michele Pinelli1, Francesco Musacchia1, Alessandra Varavallo1,2, Margherita Mutarelli1,3, Sandro Banfi1,2, Angelo Selicorni4, Milena Mariani4, Silvia Maitz5, Valeria Capra6, Andrea Accogli6, Marcello Scala6, Vincenzo Leuzzi7, Anna Commone7, Francesca Nardecchia7, Serena Galosi7, Mario Mastrangelo7, Donatella Milani8, Corrado Romano9, Pinella Failla9, Donatella Greco9, Chiara Pantaleoni10, Claudia Ciaccio10, D'Arrigo Stefano10, Nicola Brunetti-Pierri1,11, Giancarlo Parenti1,11, Gerarda Cappuccio1,11, Andrea Ballabio1,11, Antonietta Coppola12, Martino Montomoli13, Maria Alice Donati14, Teresa Mattina15, Marcella Zollino16, Simona Amenta16, Albina Tummolo17, Claudia Santoro18, Giulio Piluso2, Valerio Bonolis2, Roberta Zeuli2, Giancarlo Blasio2, Daniele De Brasi19, Francesca Del Vecchio Blanco2, Angela Peron20, Gennaro Oliva21, Diego di Bernardo1,22, Ermanno Rizzi23, Giorgio Casari24,1, Vincenzo Nigro1,2 1Telethon Institute of Genetics and Medicine, Pozzuoli, Naples, Italy, 2Department of Precision Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy, 3Institute of Applied Sciences and Intelligent Systems "Eduardo Caianiello", ISASI, National Research Council, Naples, Italy, Pozzuoli, Naples, Italy, 4Department of Pediatrics, ASST Lariana Sant'Anna Hospital, San Fermo della Battaglia, Italy, 5MBBM Foundation, Monza, Italy, 6Neuroscience Department, Giannina Gaslini Institute, Genoa, Italy, 7Department of Human Neuroscience, Sapienza University of Rome, Rome, Italy, 8Pediatric Highly Intensive Care Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy, 9Oasi Research Institute - IRCCS, Troina, Italy, 10Developmental Neurology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, 11Department of Translational Medicine, Section of Pediatrics, Federico II University, Naples, Italy, 12Department of Neuroscience and Reproductive and Odontostomatological Sciences, Federico II University, Naples, Italy, 13Pediatric Neurology, Neurogenetics and Neurobiology Unit and Laboratories, Neuroscience Department, A Meyer Children's Hospital, University of Florence, Florence, Italy, 14Metabolic and Muscular Unit, Regional Reference Centre Expanded Newborn Screening, Meyer Children Hospital, Florence, Italy, 15Department of Biomedical and Biotechnological Sciences, University of Catania, Catania, Italy, 16Institute of Genomic Medicine, Catholic University, Gemelli Hospital Foundation, Rome, Italy, 17Department of Metabolic Diseases, Clinical Genetics and Diabetology, Giovanni XXIII Children's Hospital, Bari, Italy, 18Pediatric Surgery, Department of Women, Children, General, and Specialist Surgery, Campania University "Luigi Vanvitelli", Naples, Italy, 19Department of Pediatrics, AORN Santobono Pausilipon, Naples, Italy, 20Child Neuropsychiatry Unit-Epilepsy Center (Service of Medical Genetics), San Paolo Hospital, Department of Health Sciences, Università degli Studi di Milano, Milan, Milan, Italy, 21Institute for High Performance Computing and Networking, National Research Council, Naples, Italy, 22Department of Chemical, Materials and Industrial Production Engineering, University of Naples Federico II, Naples, Italy, 23Fondazione Telethon, Milan, Italy, 24Vita-Salute San Raffaele University, Milan, Italy. P12.047.C Detection of T315I in patients with Chronic Myeloid Leukemia by ddPCR preliminary results Hristo Y. Sánchez Holgado: None. In this presentation we focus only on the heterozygous mutations found in PTPN11. Herranz-Cecilia: None. "Programmi di Ricerca 2018-2020", Istituto Pasteur—Fondazione Cenci Bolognetti (to F.C.); "Progetti per Avvio alla Ricerca - Tipo 1", Sapienza University of Rome (to E.D'A.). Patients with RSTS mainly exhibit distinctive facial features, broad and often angulated thumbs and halluces, intellectual disability, and postnatal growth retardation. Uebe: None. Ereminienė: None. Additional qRT-PCR, reveals inhibition of Bcl-2 and TP53, along with the overexpression of TGFβ1, for both cell lines. Depending on the number and type of genes, the KIR genotype of women (AA, AB and BB) was established. Esteve: None. Conclusions: Stress in students during exams induces oxidative stress and significant f-SatIII and TR content fluctuations in DNA against stable ribosomal repeat content background. Tyler-Smith: None. Experimental validation of the effect of variants on splicing was performed using minigene and RNA analysis. Saavalainen: None. Bakavicius: None. Tisserant: None. A gene was considered differentially expressed in smokers' CCs versus control CCs when showing a fold change >1.4 or A (p.Asp4543Gln), c.11375C>T (p.Pro3792Leu) and c.8788C>T (p.Pro2930Ser), the IDH1 c.565A>G (p.Ile189Val) and the KDM6B c.2282C>G (p.Thr761Ser) missense variants were predicted as VUS (variants of uncertain significance). Peron: None. WINGS is the first commissioned, diagnostic rWGS service for acutely unwell children in the UK National Health Service. Kurppa: None. A trio- or single based whole genome sequencing (WGS) (Illumina NovaSeq 6000 platform) approach, and a standard karyotyping were undertaken analyzing DNA from peripheral blood. Materials and Methods: We chose a model of psychoemotional stress experienced by the second year medical students during the exams. Cavaillé: None. Introduction: Congenital erythrocytosis is a rare haematological disorder with abnormally high erythrocyte count. PCR amplification of exons 1 and 9 of the CRPPA gene (chromosome 7) was performed. Consultant/Advisory Board; Modest; Genomic Strategy, OncoDNA cancer theranostics, Karus therapeutics, Cambridge Cancer Genomics. Rochat: None. Variants were determined using minimap2 alignments along with a custom SQL database for characterizing and reporting results. Gligorov: F. Conclusion: The genetic contributions to POP remain poorly understood. M.F.C.M. Knapen: None. Wojcik3,4, Anne O'Donnell-Luria3,4, Katrin Õunap1,2 1Department of Clinical Genetics, Institute of Clinical Medicine, University of Tartu, Tartu, Estonia, 2Department of Clinical Genetics, United Laboratories, Tartu University Hospital, Tartu, Estonia, 3Broad Institute of MIT and Harvard, Broad Center for Mendelian Genomics, Cambridge, MA, USA, 4Division of Genetics and Genomics, Boston Children's Hospital and Harvard Medical School, Boston, MA, USA. Radoi: None. However, up to date the molecular basis for cutaneous manifestations in CS is largely unknown. P11.060.B HHAT-related multiple congenital anomalies: Report of an additional family and delineation of the syndromeShruti Pande1, Periyasamy Radhakrishnan1, Naveenchandra M. SP-4503.2021.4) to Y.A.B., and D.O. Ott Research Institute of Obstetrics, Gynaecology and Reproductology, project 558-2019-0012 (AAAA-A19119021290033-1) of FSBSI. Szlepák: None. Ferretti: None. SLC7A8 encodes for the L-type amino acid transporter 2 (LAT2) and LAT2 immunohistochemistry of osteosarcoma tissue suggested improved prognosis for patients with higher LAT2 expression (p = 0.082). Siermann: None. Patients showed a digenic or compound heterozygous inheritance of RAS pathway hypomorphic variants, singularly present in healthy parents (PMID: 32514133). Maximova: None. Zechi-Ceide 1, Nancy M. Millat: None. Clear cell renal cell carcinoma (CCRCC) is the most common renal cancer whose prognosis is currently assessed by imperfect clinical scores. The BTK gene associated with pathology has more than 500 mutations, including single base pair substitutions, splicing defects, and small deletions and insertions. Introduction: Copy number variants (CNVs) play important roles in the pathogenesis of several genetic syndromes. Kutsev1, Rena A. Introduction: By February 2021, 108 million people had been infected by SARS-CoV-2, a disease associated with a worldwide 2.2% mortality rate. It was a 48-year-old woman presented with: joints hypermobility, recurrent dislocations, whole body pain, easy bruising, striae, gothic palate and arachnodactyly. CMA was used on amniotic fluid cells to detect copy number variants. High risks of trisomies by NIPT were confirmed in 66/70 cases for trisomy 21,in 22/23 cases for trisomy 18 and in 4/4 cases for trisomy 13. F.D. Costa: None. Previously, SCN9A gene variants, in particular the c.1921A>T p.(Asn641Tyr) substitution, have been defined as likely autosomal dominant causes of febrile seizures plus and other monogenic seizure phenotypes indistinguishable from those associated with SCN1A. Conclusions: The results of clinical validation demonstrate a very good diagnostic parameter of the GeneProof assays and together with myCROBE® Fully Automated Instrument proved to be very convenient and time-saving tool for testing of thrombophilic mutations in clinical routine. Polonikov: None. WES approach appears powerful in mutation detection and in revealing new genotype-phenotype association. Results: The frequencies of the variant A allele and AA genotype in the total group of patients and in the subgroup of patients with Cobb angle above 40° were significantly higher than that in the controls (p C mutation as well. Biard2, Yves Sznajer1 1Center for Human Genetics, Cliniques universitaires Saint-Luc, UCLouvain, Brussels, Belgium, 2Obstetrics, Cliniques universitaires Saint-Luc, UCLouvain, Brussels, Belgium. Francipane: None. Results: Retrospective analysis of ClinVar submissions highlighted 107.167 significant changes in variant status and a monthly median of 23 new genes associated with Mendelian diseases between July 2017 and December 2019. E.M. Inyushkina: None. A. Overall, the high prevalence of mosaicism in CdLS as well as the disparity in tissue distribution should be taken into account when molecular diagnosis and familial cosegregation studies are planned. Results: From the 452 variants identified, two were classified as pathogenic. Another heterozygous variant c.1201C>T (p.Arg401Cys rs761492029), revealed in the MYO5B gene, described as pathogenic. Furthermore, maternal preeclampsia (n = 4) or hypertension during pregnancy (n = 1) is observed in 5 of 6 cases (83%) in this family, when CS mothers carry CS fetuses. Following rounds of revision in the development, contextualisation, translation, and validation stages, the CSRI-Ra is ready for use in empirical research. Vitsios: A. Houweling2, Bertrand Isidor7,8, Ronald H. S.I. Kutsev: None. Based on position weight matrices, we predicted TF binding sites for 810 human TFs, and calculated changes of binding capacity at 28,773 DNM-sites. In conclusion, the functional profile retrieved from GSEA indicates that immune and DNA biological signatures are associated with radiotherapy-induced late toxicity. A total of seven pathogenic/likely pathogenic variants in six unrelated families (18.2% of the families) were identified. Most of the the cases (52%) are due to mutations in the PTPN11 gene, followed by the frequency of SOS1, BRAF, NF1, SHOC2 and others. Krulišová: None. We are currently working on a double knockout mouse. Results: We detected eight potentially relevant missense variants in nine patients with severe oligozoospermia or azoospermia, resulting in a detection rate of 1.0% for NR5A1 in the MERGE cohort. Renieri32,33,34, A. Conclusions: Our results show that SLC6A4 expression is increased in GTS individuals, and that this difference is more pronounced in GTS individuals with the LAC/LAC genotype. Introduction: Hereditary Haemorrhagic Telangiectasia (HHT) is an autosomal dominant vascular disorder affecting 1:5000-8000 individuals worldwide. A.C.S. Bolund: None. Pérez-Mendoza: None. Karyotype analysis showed a balanced translocation involving chromosomes 2 and 18 with breakpoints at 2q24.3 and 18q21.1. Microarray analysis detected a 181 Kb de novo microdeletion at 2q24.3, involving SCN2A gene.Optical Genome Mapping(OGM) was used to characterize the rearrangement and to verify the correlation between the 2q24.3 microdeletion and the translocation breakpoint. N.P. Babushkina: None. Kazantseva: None. Results: We achieved a global diagnostic yield of 65% (300/460), which varied depending on the clinical diagnostic group. Poirsier-Violle: None. MendelScan encodes diagnostic/screening criteria for multiple rare diseases, mapping clinical terms to appropriate SNOMED CT codes (UK primary care standardised clinical terminology) to create digital algorithms. P04.002.C A novel truncating variant in the FGD1 gene associated with Aarskog-Scott syndrome in a family previously diagnosed with Tel Hashomer camptodactylyLena Sagi-Dain1, Irena Kessel1, Amir Peleg1, Tamar Paperna2, Nina Ekhilevitch2, Alina Kurolap3, Hagit Baris Feldman3, Marina Bar-Shay 1 1Carmel Medical Center, Haifa, Israel, 2Rambam Medical Center, Haifa, Israel, 3Ichilov Medical Center, Tel Aviv, Israel. Results and Outlook: The re-analysis of 229 known cancer predisposition genes allowed solving 2-3% of GENTURIS cases. The overall incidence of both anomalies is however increasing in the Czech Republic, as more and more mothers prefer surgical intervention over the termination of the pregnancy. Mizokami: B. Physical examination revealed short stature, sparse scalp hair, macrocephaly, facial dysmorphism (down-slanting palpebral fissures, peculiar nose with broad ridge and tip and underdeveloped alae, and low-set ears), and brachydactyly. Blauwendraat: None. In 12% of solved cases, a mitochondriopathy-associated gene was found to harbor the disease-causing variant. Vuillaume: None. Sreelatha6, Jennifer A. This work aimed to explore the interplay between host genetics and the oral microbiota in two understudied populations, African Americans and Latinos. Neijzen 2, Dennis Dooijes2, Yvonne J. Cytokine gene polymorphisms were analyzed using allele-specific PCR. Funding: NSP "Young Scientists and Postdoctoral Fellows" D. We prepared the libraries in the automated liquid handler, following vendor recommended safe stop points. van Slegtenhorst1, Alice Brooks1, Robert M. Also, We found of the GG genotype was not found in both groups risk in the child and adolescent population of Rostov-on-Don were. The main cause of dMMR is somatic MLH1-promoter hypermethylation. Krizova: None. This region harbors eight segmental duplicated genomic regions termed low-copy repeats A-H (LCR22A-LCR22H) that mediate nonallelic homologous recombination resulting in rearrangements of 22q11.2. The most frequently reported are imbalances with the breakpoints encompassing LCR22A to LCR22D. Secondly, a patient diagnosed in adulthood for severe combined immunodeficiency "leaky" phenotype, showed a pathogenic variant combination involving CARD11 and STAT3 genes that was successfully ranked by DIVAs in the top five. Ratbi: None. It may reduce the need for radiation exposure and sedation in surveillance protocols. Future work will expand this study to investigate more phenotypes in 450,000 UK Biobank individuals. Ponzi: None. Results: The sample consisted of 423 nurses. Conclusion: Our results aid the understanding of molecular grounds of the clonal evolution in CLL, which is necessary for the rational use of available treatment options and for designing of suitable diagnostic panels. Antolin: None. In our study for the first time for native cells high-throughput sequencing (RNA-seq) was applied to analyze the global transcriptome of the human DSCs during uncomplicated pregnancies. Results: We discovered novel MLH1 in-frame-deletion LRG_216t1:c.2236_2247delCTGCCTGATCTA p.(Leu746_Leu749del) associated with LS. Comparing the amino acid composition of mtDNA genes between orthologs of mitochondrial genes in alpha-proteobacteria, fungi, plants, invertebrates, and five classes of vertebrates, we observed a global billion-year trend: losers become rarer while gainers become more frequent among these taxa. Twin and family studies indicate genetic factors are involved in SLI. Hypertelorism and antimongoloid eye slant, micrognathism, webbed neck, pyelonidal cyst and preaxial polydactyly both on the left foot and right hand were noticed. P11.105.C Risk of autoimmune diseases in patients with RASopathies: systematic study of humoral and cellular immunity Maria Anna Siano 1, Mariateresa Falco2, Valeria Marchetti3, Stefano Pagano3, Francesca Di Candia3, Daniele De Brasi4, Alessandro De Luca5, Valentina Pinna5, Simona Sestito6, Daniela Concolino6, Marco Tartaglia7, Pietro Strisciuglio3, Vittoria D'Esposito8, Serena Cabaro8, Giuseppe Perruolo8, Pietro Pietro Formisano8, Daniela Melis1 1Postgraduate School of Pediatrics, Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, Salerno, Italy, 2Pediatric Unit, San Giovanni di Dio e Ruggi d'Aragona University Hospital, Salerno, Italy, 3Postgraduate School of Pediatrics, Faculty of Medicine University of Naples Federico II, Naples, Italy, 4Unit of Pediatrics, AORN Santobono-Pausilipon, Naples, Italy, 5Molecular Genetics Unit, Fondazione Casa Sollievo della Sofferenza, IRCCS, San Giovanni Rotondo, Foggia, Italy, 6Department of Medicine, University "Magna Graecia", Catanzaro, Italy, 7Genetics and Rare Diseases Research Division, Ospedale Pediatrico Bambino Gesù, Rome, Italy, 8Department of Translational Medical Sciences, University of Naples Federico II & Institute of Endocrinology and Experimental Oncology, National Research Council, Naples, Italy. D.C. Tekguc: None. Sitek: None. L.B. Ousager: None. The main facial features were: trianglar face, arched/thick/unusual eyebrows, low nasal bridge, anteverted/thick nares and long/smooth philtrum. Correia Guedes: None. V.V. Kadyshev: None. The mutation analysis of GAA gene was performed with Sanger sequencing and MLPA methodology. Scharf: None. IHC outcomes were missing in 13%, germline testing was performed in 76% of eligible patients. Emotional and behavioral outcomes have been assessed using PSC and ABC-C scores. Introduction: Using mouse genetic studies, we set out to identify which of the 30 genes causes brain size and other NeuroAnatomical Phenotypes (NAPs) at the autism-associated 16p11.2 locus, independently in male and female. P17.013.D A cancer genomics reference resource and implementation toolkit around GA4GH standardsQingyao Huang1, Bo Gao1, Rahel Paloots1, Paula Carrio-Cordo2, Ziying Yang1, Michael Baudis 1 1University of Zurich, Zürich, Switzerland, 2Paula Carrio Cordo, Zürich, Switzerland. Patients with pathogenic variants had significantly lower event-free survival compared to genotype-negative DCM patients. P01.061.A NIPD for translocation carriers - yes please or no go? We identified markers of osteoarthtis progression combining gene and transcript-level analysis for the first time. MLPA analysis of the Xq21 is implied. Funding: Instituto de Salud Carlos III (CD19/00231, FI17/00177, PI17/00610, PI20/00876), Ministerio de Ciencia e Innovación (RTC-2017-6471-1; AEI/FEDER, UE), and agreement OA17/008 with ITER; ECIT CGIEU0000219140. Simkus: None. In addition, one female specific locus was identified. Tissue-specific interactomes source: HumanBase. We observe moderate correlation of scores (0.72) between genome builds, which we ascribe to the changes in the feature sets as well as adjustments in feature importance. Moderate-to-severe high-frequency sensorineural hearing loss was diagnosed at approximately six years of age. Materials and methods: Prospective and observational study started in September 2019. Conclusion: This study helps to show that a customized gene panel is the method of choice for studying patients with ADPKD and further emphasizes the genetic variability of this condition. A.V. Bocharova: None. WES analyses were guided by HPO terms and custom gene panels based on literature. Santa Marina: None. She had mild insufficient dysplastic atrioventricular valves and joint hypermobility. P06.020.A Recurrent hydrops fetalis, a long journey to diagnosis Sana Skouri 1, Ines Ouertani1, Soumeya Bekri2, Catherine Caillaud3, Ridha M'rad1 1Departement of Medical Genetics, Charles Nicolle Hopistal, Tunis, Tunisia, 2Department of Metabolic Biochemistry, Rouen University Hospital, Rouen, France, 3Biochemical, Metabolomic, and Proteomic Department, Necker University Hospital Group, Paris, France. Pizzuti: None. Conclusions: These gene-edited organoids could be an ideal model for the development of a gene therapy for DAAT. The major research question: What are the f-SatIII and TR CNVs in human leukocyte as a function of psychoemotional stress. All authors work in a Unit supported by UK Medical Research Council (MC_UU_00011/1&4). Applying our workflow for testing 180 markers on 1000 cfDNA samples enabled definition of a robust and highly reliable diagnostic methylation 12-plex classifier of AUC 0.88. Prieto-González: None. The case report may help geneticists and oncologists to better understand the clinical and genetic heterogeneity of BHDS in various populations. EasyQC was applied in order to unify and harmonize datasets. Kathom: None. Specific cardiovascular diagnoses were considered too difficult for laymen. Introduction: Direct-to-consumer genetic tests (DTC-GT) can provide health-related information outside clinical care pathways and are widely available. Haack6, Irina Hüning14, Ralf A. RNA-seq detected 90% of fusion events that were reported by routine with high evidence, while samples in which RNA-seq failed to detect fusion genes had overall lower and inhomogeneous sequence coverage. The proband's paternal uncle has HCM and previously had a normal HCM gene panel through his Cardiology team. Introduction: There are approximately 7,000 rare diseases affecting 350 million people worldwide. Of note, two EVC recurrent deletions were identified, affecting 4 and two patients respectively. We additionally investigated explained variance in age and sex-specific subgroups. Alekseeva: None. Consequently, detected of chromosome aneuploidies in samples from products of conception is a key part of the investigations of reproductive failure in humans. When introducing PGS into the health system, it is important to strengthen the knowledge of the population of PGS. Vičić: None. For the polymorphism of TLR9, statistically significant differences were found in the distribution of allele ($\chi 2 = 8.161$; $p = 0.005$) and genotypes ($\chi 2 = 7.538$; $p = 0.024$) frequencies. The FAT4 gene encodes a protein that is a member of protocadherins. Consultant/Advisory Board; Modest; Medtronic, Lumicell, ImpediMed. P24.013.D Genome-wide association study of estradiol levels, and the causal effect of estradiol on bone mineral density Daniel Schmitz, Weronica E. Conclusion: We report a familial case of Acromicric dysplasia, with a novel variant in FBN1 gene. Molecular diagnosis in LCA is of particular importance in clinical decision-making and patient care since it can provide ocular and extraocular prognostics and identify patients eligible to developing gene-specific therapies. With the confirmatory results on the known tumor promoting genes, this work has a potential to identify novel functional pathways that are exerted through CNV. T.O. Kilpeläinen: None. Mitne-Neto: A. Rodríguez-Hidalgo: None. Torun1, Pei Zhao2, Yahong Kang2, Sebiha Çevik1, Oktay I. Additionally, visualization of predictive CpGs demonstrated that dependent CpGs are automatically pruned and that independent signals can be assigned to biologically regulatory elements. Extermann: A. Table 1: Frequency of the different impairment in patients with brachydactyly type C cohort patients percentage literature patients percentage Angel-Shaped Phalango-Epiphyseal Dysplasia 22/63 34.9% 5/27 18.5% 1st rays brachymetacarpy 49/63 77.8% 16/27 59.3% 2nd rays brachymesophalangy 51/63 81% 18/27 66.7% 3rd rays brachymesophalangy 36/63 57.1% 13/27 48.1% 5th rays brachymesophalangy 47/63 74.6% 19/27 70.4% 2nd rays brachybasophalangy 14/63 22.2% 8/27 29.6% 3rd rays brachybasophalangy 14/63 22.2% 10/27 37% 2nd rays clinodactyly 22/66 33.3% 17/30 56.7% 3rd rays clinodactyly 14/66 21.2% 11/30 36.7% 5th rays clinodactyly 43/66 65.2% 17/30 56.7% polyphalangy 19/63 30.2% 9/27 33.3% pseudoepiphyses 16/63 25.4% 6/27 22.2% foot damage 20/49 40.8% 11/26 42.3% heightG, p.I269R) in the coding region of the HDAC8 gene, which was predicted to be pathogenic. Conclusions. The hs-MSI tool detected MSI in non-neoplastic tissues from CMMRD individuals regardless the tissue origin. Karakac: None. Benke: None. The study was supported by European Regional Development Fund Project No 1.1.1.2/VIAA/2/18/287. K.M. Girisha: None. Carrabba: None. NC_000023.10:g.(153,744,322_153,759,773)_(153,793,401_153,798,250)del. Queralt: None. Historically, testing costs and clinical implementation challenges led to restrictive testing guidelines in many countries. The DNA analysis showed that patient is a heterozygous carrier of the CTC deletion in exon 9 of the ANKH gene, resulting in a serine deletion at position 375 (rs121908406_c.1122-4delCTC_p.Ser375del). Her mother was again pregnant, and a fetal echocardiogram had been suggestive of right ventricular hypertrophy. NGS technologies (WES and WGS) are effective tools to facilitate the identification of affected patients. Duplication of 7p is rarely described in the literature, with variable phenotypic spectrum depending on mosaicism and duplicated region. This is a molecular genetic screening test to identify variations in the number of copies (deletions / amplifications) of 37 sequences in the 5q13 region. However, as family history was not initially available, the entire NF1 coding sequencing and MLPA was performed. Sosnina: None. Mixed populations of both normal and mutant mitochondrial DNA can coexist in a single cell (heteroplasmy). 39% of TBMN cases had a reported family history in contrast to 78% in AS cases (p = 0.006). Opalic: None. c.933+3A>C p? Studies of the deficiency of GW182 in mice and its orthologue gawky in Drosophila demonstrated defects in embryonic development. The glycoaminoglycans profile in the amniotic liquid was abnormal, though not specific of a particular MPS. Thirty patients with ancestry from Southern or Central Portugal, or with known or assumed African ancestry performed hemoglobinopathies screening. Materials and Methods: We report a case of a 1-year old male patient presenting in our genetic counselling unit with speech and motor developmental delay, hydrocephalus and hypertrophy of the choroid plexus with consecutive ventriculomegaly. Together, our results suggest that the genome of healthy centenarians is enriched with a constellation of variants each exerting small advantageous effects on aging-related biological mechanisms that maintain overall health and decrease the risk of age-related diseases. We describe three cases in which it allowed an exhaustive molecular diagnosis. To determine whether N-glycosylation PTM is regulated by the same genetic mechanisms in different proteins, we performed genome-wide association meta-analysis of glycosylation of two proteins - transferrin (35 N-glycan traits, N = 1890) and immunoglobulin G (IgG) (24 N-glycan traits, N = 2020). Gene Relative pancreatic expression (RQ) Ins1 0.1 ABCC8 0.21 KCNJ11 0.32 Gck 0.54 After KD with Vitamin D, we revealed an increase in pancreatic expression of Insulin gene compared to group of KD only (RQ = 0.35), not reaching the level in controls. Women who agreed to carry out an IPT, compared with those who decided not to carry out an IPT, more often noted the importance of obtaining the most complete and early information. Conclusions: The most distally located genes play a determining role in the phenotypes of terminal 6p deletions. Nordgarden: None. We will assess the heritability of the aging rate and measure the importance of environmental factors for accelerated aging. Haplotype CDTGCC was marginally associated (p = 0.07) with reduced risk of breast cancer in non-obese patients as compared with non-obese controls where as haplotype AICGTC was marginally associated (p = 0.09) with reduced risk of breast cancer in obese patients when compared with non-obese patients. Rosenfeld11, Cynthia Curry12, Laurence Faivre13,14, Anja Leiber15, Scott Robinson16, Richard S. Ali1, Sarah M. Sequencing germline data were filtered to select variants with plausible pathogenicity, rare frequency and previously involved in cancer. van Karnebeek1 1Radboudumc, Nijmegen, Netherlands, 2Amsterdam UMC, Amsterdam, Netherlands, 3University Medical Center Utrecht, Utrecht, Netherlands. te Paske 1, José Garcia-Pelaez2, Anna K. Maternal immunotolerance is provided by the interaction between the cells of the maternal immune system in the uterus (uterine NK cells) and the embryo. Conclusion: In our opinion, the normative legal regulation in this area needs to be expanded and brought into line with international legislation. Conclusions: Our study identified frequency of SNP in prostate cancer patients. Foulkes10, Clare Turnbull11, Helen Hanson11, Steven Narod12, Banu K. Purpose: To generate a PRS to estimate the risk of AF in a Hispanic/Latino cohort. Employment (full or part-time); Significant; Mendelian Ltd. Methods: Prevalence of heterozygous microdeletions in OTOA and STRC genes, as well as deletions in the DFNB1 locus encompassing GJB6 gene, was determined using electronic database of Rabin Medical Center. Hoenicka: None. Frayling: None. The exomes of AD patients contain 4 pathogenic variants in these genes including the APOE-ε4 allele. Our study demonstrates that the EDS technology is mature enough to support genomics and life science applications, and holds the promise to revolutionize access to synthetic DNA — particularly in settings where in-house synthesis and fast iteration translates to tangible advantages. Results: There was a significant effect of PRS on amyloid rate of change when using the more stringent thresholds for SNP inclusion: pT = 5x10-8: β = 0.0054 (CI: 0.000042-0.011), p = 0.048; pT = 1x10-5: β = 0.0056 (CI: 0.0000785-0.011), p = 0.047. Manning1, David McGaughey2, Vinod Sharma1, Graeme C. A secondary analysis comparing VAF in the proband and apparently unaffected parents can be used to identify these inherited 'de novo' variants in clinically relevant genes. Results: Three genome-wide significant loci were identified (rs1491985, rs10490825, rs165599) residing within the genes RNF123, ATP2C1, and COMT. This powerful tool, however, does not always provide a diagnosis if it is not supported by clear clinical and/or biochemical markers. Maitre: None. Prat: None. PJS is characterized by mucocutaneous pigmentation and hamartomatous polyps, predominantly affecting the small intestine. May: None. Recent advances in optical genome mapping (OGM) have the potential to address these shortcomings. Tayal: None. Massier: None. Group of dislipemias of genetic origin and metabolic diseases, IdiPAZ, Hospital Universitario La Paz, Madrid, Spain., Madrid, Spain, 2Department of Internal Medicine, Hospital de la Princesa, Madrid, Spain., Madrid, Spain, 3Internal Medicine Service, Hospital Carlos III, HULP, Madrid, Spain., Madrid, Spain, 4Next Generation Sequencing Section. Methods: Molecular analysis showed a new hemizygous mutation p. Median survival time of patients with this type of brain tumor is about 15 months despite current therapeutic strategies including surgery, radiotherapy and chemotherapy. Kheirkhah: None. For this purpose, genomic analysis is applied together with deep phenotyping in a multidisciplinary approach involving clinicians, geneticists, bioinformaticians and researchers. Eldar-Geva: None. Picchiotti: None. Paraboschi: None. Kremensky: None. Three adult siblings with the c.757delG homozygous variant exhibited phenotypic variability, as only one of them reported symptoms whereas the others were asymptomatic. Yousef: None. Chirita-Emandi: None. Touraine: None. Sarkar: None. This solution consists of 116,355 individually designed probes that span approx. Büki: None. M.A. AlBalwi: None. Conclusion: Our findings suggest an association between the type of the RPE65 carried variant and the AAO, providing useful data for clinical management of these patients. SOX3 transcription factor is key regulator of cell fate decisions in numerous developmental processes. Topçu: None. R.J.T. van Golde: None. We aim to review the findings of the genetic counseling of a cohort of patients at our public gametes bank. His younger sister died in the 32nd week of gestation. Supported by grants from the ISCIII and FEDER (PI18/00507) and BEGISARE. Introduction: SOX4 (OMIM:184430) is a transcription factor with pleiotropic functions required for developmental processes such as corticogenesis. Since polygenic causes and mutations in known HBM genes had been previously discarded, we searched for rare causal variants in novel genes by whole-exome sequencing in two affected and one non-affected family members. Conclusions: This study demonstrates the utility of panel testing for patients with a suspected skeletal dysplasia or growth disorder, with diagnostic yield of 42%. Just seven genes were responsible for the majority of diagnoses. Hammarström: None. Conclusions: Our results indicate that the dysregulated inflammation observed in PD patients affects APCs by inducing the production of pro-Th17 cytokines. Introduction: Endometriosis is a common gynecological disorder in which the endometrium grows outside of the uterus. Omata: None. Segregation analysis and mRNA studies for functional evaluation are in course. The aim was to determine the contribution of the GJB2 gene to the hereditary sensorineural hearing loss (HSNHL) incidence in Ossetians, including Ironians and Digorians, the main subethnic groups, from North Ossetia-Alania. Conclusion: We present the fifth index case of molecularly proven PPCD1. While rs2106809 was associated with an increased risk of being hospitalized (T/T vs. Conclusions: Based on family and clinical history, type 2 alpha mannosidosis was confirmed in the siblings with novel compound heterozygous mutations classified as pathogenic. Materials and Methods: Relative mRNA expression of TRAIL pathway inhibitors (DcR1, DcR2, cFLIP, XIAP, BCL2, BCL-XL, MCL1) was evaluated in 90 breast cancer tissues, using the RT-PCR/ΔΔCt method. Baranova: None. van den Boogaard1, Aebele Mink van der Molen1 1Wilhelmina Children's Hospital, University Medical Center, Utrecht, Netherlands, 2Erasmus University Hospital, Rotterdam, Netherlands, 3Leiden University Medical Centre, Leiden, Netherlands, 4Amsterdam University Medical Centre, Amsterdam, Netherlands,

5Maastricht University Medical Center, Maastricht, Netherlands, 6Amsterdam University Medical Center, Amsterdam, Netherlands, 7University Medical Center Groningen, Groningen, Netherlands. Employment (full or part-time); Significant; NIMgenetics. Conclusion: Our data suggest that when studying the effects of regulatory peptides on the transcriptome under pathological conditions, it is necessary to consider their effects under normal physiological conditions. Patients and Methods: 48 HBOC cancer Patients were screened for mutations using the On-Demand Research Assay. Bykonya: None. Faivre11,12, S. Moreover, another issue when working with cell lines is the possible contamination or misidentification of the cell lines. Acuña-Alonzo: None. P.D. Rohde: None. Wain, Edward J. Meagher: None. Jurj: None. Slí: None. Conclusion: 1. 15% chose the absence of relatives with hereditary diseases as a reason for refusal. For this reason, a CVS was performed and the fetal microarray revealed an interstitial deletion in the 1q21.1 region. Remarkably, the potential loss-of-function mutation results in a non-lethal phenotype in our patients. The same variant was found in heterozygosis with 34% mosaicism rate in the mother. Parikh: None. This can impact the age of onset in both the current and successive generations. Klovins: None. Furthermore, we also identified genetic variants that could mediate in those associations, allowing future functional experiments. de Leeuw: None. H.S. AlQudairy: None. We present a study cohort composed of individuals carrying the same uncharacterized RYR1 heterozygous missense variant but who demonstrate extremely diverse phenotypes ranging from exertional rhabdomyolysis, fixed weakness with ptosis, and asymptomatic individuals. Combined with the results of the literature, these rare findings concerned both single nucleotide variants and copy number variations. Cisneros-Barroso: None. We present a case of a prenatal conspicuous microcephaly linked to two novel mutations in the PHGDH gene likely associated with NLS1. This resulted in a precompiled dataset of interspersed repeats within coding regions of the human genome. Ivanov: None. P24.055.B High-resolution genetic maps provide new insights into mitochondrial dysfunction in Type 2 diabetes Hannah Maude 1, Winston Lau2, Nikolas Maniatis2, Toby Andrew1 1Imperial College London, London, United Kingdom, 2University College London, London, United Kingdom. Random and Local inbreeding Population Random inbreeding Local inbreeding Sity Vladikavkaz 0.00029 0.000024 Pravoberezhniy raion 0.00058 0.000152 Ardonskiy raion 0.00069 0.000327 Digorskiy raion 0.00088 0.000394 Irafskiy raion 0.00120 0.000587 Prigorodniy raion 0.00101 0.000084 Alagirskiy raion 0.00076 0.000192 Kirovskiy raion 0.00095 0.000333 Mozdokskiy raion 0.00018 0.000095 Random inbreeding ranged from 0.00018 in Mozdokskiy to 0.00120 in Irafskiy raion with average 0.00073. Haplotype analysis showed a founder origin in the majority of patients. Santer: None. Pruunsild: None. A larger sample size is required to validate these results. NIPT uptake in socioeconomically disadvantaged neighbourhoods was 20.3% whereas NIPT uptake in other neighbourhoods was 47.6% (p A) in STXBP1 gene (NM_003165.6). Antoniadou: None. The study showed a ≈5Mb genomic duplication of band 8p23.1 that did not run into euchromatic variants and it modified the dosage of SOX7 and GATA4 genes.Patients with duplication of band 8p23.1 show a diversity of clinical findings.There are debates about the relationship of the duplicated GATA4 gen and congenital genetic defects in these patients. WES was also performed in nine tumor samples to analyze the somatic profile. We analyzed the relationship between the degree of pleiotropy of variants and the intensity of background selection (selection against deleterious mutations) across the human genome. Cannaerts: None. Kobayashi: None. Bell3, Kumarasamy Thangaraj1,2,6 1CSIR-Centre for Cellular and Molecular Biology, Hyderabad, India, 2Academy of Scientific and Innovative Research, Ghaziabad, India, 3Department of Twin Research & Genetic Epidemiology, King's College London, London, United Kingdom, 4Ladakh Institute of Prevention, Leh, India, 5Department of Applied Zoology, Mangalore University, Mangalore, India, 6Centre for DNA Fingerprinting and Diagnostics, Hyderabad, India. Rančelis: None. Manunta18, G. Mutation analysis of parents and grandparents found both parents and the paternal and maternal grandmothers to be carriers but no evidence of consanguinity as they come from very distant parts of Spain. Nicolas: None. Guzmán-Aguilar: None. We describe a 5-year-old girl with a heterozygous pathogenic variant [c. P06.056.A A recessive mutation in TFAM causes mtDNA depletion associated with primary ovarian insufficiency, seizures, and hearing loss Farid Ullah 1,2, Waqar Rauf1, Kamal Khan2, Sheraz Khan1, V Oliveira3, K Bell4, M Tariq1, S Bakhshalizadeh4, T Philippe5, A Sinclair4, E Tucker4, S He6, S M. Goncu: None. Hooning, Linda Broer, Willemina R. Domingo Gallego: None. Methods: Two affected members of a family diagnosed with dominant retinitis pigmentosa (adRP) underwent whole-exome sequencing (WES). Revazyan1, Alexey N. In an attempt to establish the diagnosis Whole exome sequencing was carried out. Carvalho1,5, Richard A. 1741A>Gp. (Asn581Asp)] in BRAF gene.The patient presents typical dysmorphic features (thin and curly hair, bilateral epicanthum, macrostomia, macroglossia), congenital heart defects (atrial septal defect, pulmonary valve stenosis), and moderate developmental delay. I.H. Kaya: None. Furthermore, despite high overall concordance, our data revealed considerable differences in the calling of (likely) pathogenic HGMD/ClinVar variants. Kalanithy2, Haktan B. Our results showed: 1) a significant hypomethylation in placenta compared to cord blood (including LINE-1, promoters, CpG islands, gene bodies, and tilings); 2) a more pronounced LINE-1 hypomethylation in placenta of small for gestational age neonates; 3) similar methylome profiles among cord blood samples, whereas they were variable in placenta, suggesting a placental broader plasticity compared to the fetus. Results: The minigene assay allowed to assess the effect(s) on splicing for all the variants we examined and showed the coexistence of multiple mechanisms of splicing alterations for seven of them. Introduction: Rare diseases (RD) with its genetic background may affect up to 6-8% of the Europeans. Employment (full or part-time); Significant; Purigen Biosystems, Inc.. Bacterial identification and susceptibility testing were performed using modern methods from the microbiology section. Banfi: None. Abu-Shatya: None. Pregnancies with marker chromosomes were terminated in 20% of the cases. Mongelli: None. We tested TISSUE-informed collapsing analysis compared to standard collapsing analysis across 1,170 cardiovascular traits using exome data for 268,450 individuals from the UK Biobank. Still, the diagnostic yield of genetic testing varies between 24-68%, depending on patient inclusion criteria, whether trio's are studied, patient's phenotype(s) and analysis strategies. Materials and Methods: Three independent cohorts with European ancestry (Spanish with MD, Swedish tinnitus and European with generalised epilepsy) were selected to sequence patients with severe tinnitus. Fuente-Revenga: None. Steinborn: None. Candayan: None. Õunap: None. Methods: Clinical data was collected from the patient's medical record and compared with literature. The analysis has been performed on UK Biobank imputed genotype counts (273,440 samples for training and 135,444 samples for test, filtered for British ancestry). For men is recommended only prostate surveillance (87,2%). Conclusions: The open-source Genome Alert! method (could enable the systematic reassessment of genomic data in a clinical routine, thus improving diagnostic yield and robustness in genomic medicine. Material and Methods: TWIST1 and EFNB1 genes were sequenced by using Sanger sequencing. Clinical data were compared with literature cases. Valcorba: None. Developmental disorders are extremely heterogeneous, but typical clinical features reminiscent of recognizable OMIM syndromes, associated with well-known causative genes, represent a valuable help in the identification of causative genetic variants. We performed two-sample Mendelian randomization (MR) to evaluate the causal effects of BMI and 14 previously hypothesised molecular risk factors (including fasting insulin (FI), bioavailable testosterone, sex hormone-binding globulin (SHBG)) on endometrial cancer risk (12,906 cases, 108,979 controls). Coutton: None. M.T. Neves: None. A.C. Ceylan: None. Rubben: None. Each trait pair included non-overlapping GWAS datasets on "VVs of lower extremities" (I83 ICD-10 code) and "Gonarthrosis" (M17 ICD-10 code) gained from different biobanks. Results: Our SMASH version detected larger CNV aberrancies (up to 500.000 bins/genome with mean bin length of 5.256 bp) and distinguished breast cancer cells from the lymphoblastic cells in a fast (runtime about one hour), inexpensive (WGS coverage required: less than 0.7) and reliable (high concordance between cells from the same cell line, good concordance with results from PacBio sequencing) way with flexible resolution. Milh: None. One unforeseen consequence of this effort was a global bottleneck in synthetic DNA supply, which currently relies on highly centralized phosphoramidite-based production and third-party logistics. Costanza: None. Introduction: Lynch syndrome (LS) diagnostics is based on the detection of DNA-mismatch-repair (MMR) system deficiency. Our study underlines also the importance of integrating complementary approaches to address the complexity of molecular networks. Disease-causing variants encompass loss-of-function (n = 168), variants predicted to affect splicing (n = 49), missense variants (n = 29), inframe indels (n = 6), and large intragenic deletions or duplications (n = 6) or entire gene deletions (n = 16). Out of those, four patients had initial and one follow up diagnosis. Dutra: A. R.M. Zechi-Ceide: None. Alsaleh: None. Exploring the enrichment of differentially expressed genes and transcripts we detected terms related to extracellular matrix, metabolism and spliceosome formation as well as new pathways gained from transcript-level analysis including collagen related terms. Mutations in several genes in this pathway have been associated with inherited GPI deficiencies (IGDs) with a wide spectrum of clinical features. P09.115.D Novel variants identified in the rare undiagnosed families Farzane Zare Ashrafi 1, Fatemeh Peymani1, Marzieh Mohseni1, Sanaz Arzhangi1, Mohammad R. It has a large range of symptoms depending on age of onset, thus making it difficult to diagnose. Bal: None. The ratios were as: trisomy 21 (49.42%), trisomy 18 (18.49%), monosomy X (9.24%), trisomy 13 (6.64%), Triploidy (4.62%), Klinefelter Syndrome (3.46%), Trisomy X (1. Sequencing revealed in the affected girl two mis-spliced transcripts: both lacking exon 3 and presenting a non-canonical isoform of exon 4, and one showing a partial retention of intron 2. For AMY2A/2B, higher copy numbers also showed a positive association ($P = 4.6x10^{-3}$). Tiosano: None. Brüggemann: None. Funding: MoH GR-2016-02363997; FRRB ERAPERMED2018-233 FindingMS GA 779282. A total of 536 patients with a clinical suspicion of NF1 were genetically tested. Correlation of clinical parameters and CMA results was assessed using Pearson chi-square and Fisher's Exact tests. In the CAS group 103 cases have dg. Four carried the MSH2 c.1906G>C founder PV, and 3, the MSH6 c.3984_3987dupGTCA founder PV; 3 patients had the MSH6 c.3956_3957dup PV. Mutations were previously identified in 56 patients as a result of sequencing of exons of the PAX6 gene. Tumors of the left kidney were resected and diagnosed by pathologist as chromophobe renal cell carcinomas. The frequent molecular diagnoses included SCN1A (n = 17), MECP2 (n = 13) and TPP1 (CLN2) (n = 12). Assays were optimised using maternal genomic DNA, before testing cfDNA extracted from stored maternal plasma obtained from 10 weeks gestation. The outcome measures were number of diagnoses, estimated time needed for analysis, and number of variants left requiring manual interpretation. Martínez-Orga1, María Fernández-Elvira1, Victoria E. Our three patients carry two unique frameshifting variants and a novel splice variant. The results revealed that based on the percentage distribution of the specimens, the highest number of isolates for E. We associated that tract with lip thickness ratio in modern humans. In 18 of the solved cases, the pathogenic variants were SNVs, while 2 were pathogenic structural variants (SV). This study aims to characterize the molecular spectrum of PCSK9-based FH in France to analyze genotype/phenotype correlations and p.(Ser127Arg) founder effect. Various bioinformatics tools and gene sequencing databases including CADD and gnomAD were used to annotate and prioritise candidate variants. Kadyshev 1, Andrei V. E., Shaw, G. Conclusions: Most of the participants reacted positively to PGS. Currently, HRD-positivity is mainly assessed by a commercial diagnostic tests with limited transparency of the underlying algorithms. Galkina 1, Lyudmila A. The gender ratio was 44-56% between men and women. Within the Solve-RD consortium, systematic re-analysis of whole-exome sequencing (WES) data from unresolved cases with intellectual disability (n = 1,472 probands) was performed. J.E. Nail: None. Besnard: None. The combined detection of point mutations and CNVs makes WES a very useful diagnostic test for patients with hypotonia. In 33.7% (32/95) the analysis was requested as a presymptomatic testing in families with already identified TTR mutations. Sergouniotis1 1University of Manchester, Manchester, United Kingdom, 2National Eye Institute, Bethesda, MD, USA. Submitters have the option to embargo pre-publication results until publication. Results: Among 238 CRC tumors a high microsatellite instability (MSI-H) was detected in 29 (12.2%) tumors from 25 patients. Additionally, the patient had bilateral ptosis, cleft palate and asymmetric dysmorphic facial features. Finally, in vitro experiments suggested that miR-146a exerts a protective effect through negative regulation of inflammation by suppressing IRAK1 and TRAF6. Speakers Bureau/Honoraria (speakers bureau, symposia, and expert witness); Modest; Genome Medical, Maze Therapeutics, Pfizer. K.B.M. Claes: None. Bioinformatic analysis was conducted using miRPathDB2 tool. Renal and urinary anomalies, umbilical hernia, organomegaly and increased cancer risk typical for IC1-GoM cases were observed in IC1-GoM patient. Results: We found an enrichment of rare missense variants in 24 synaptic genes including AKAP9, ANK2 and TSC2 (p G deep intronic change). TBP is a candidate gene for ID and is linked to PDCD2 and PSMB1 in a conserved manner, suggesting a potential interaction between these genes. Overall, our data improves 3'UTR annotation and provides novel insights into the mRNA-RBP interactome in the human brain, with implications for our understanding of neurological and neurodevelopmental diseases. Methods: Synthetic nasal matrix was spiked in with different concentrations of heat-inactivated SARS-CoV-2, and RNA was extracted using RNAdvance Viral kit on the Opentrons platform. Patients with single and complex patterns were on imatinib (45% vs. Additional defects were detected in single families in: ACTC1, ACTN2, DES, EYA4, HCCS, KCNQ1, PRDM16 and TAZ genes (Barth syndrome). Abad-Perez1, Sarina Schwartzmann1, Denise Horn1, Malte Spielmann4,5, Stefan Mundlos1,2, Martin A. Hamed1, Maha A. Introduction: Urinary exosomes, especially microRNAs (miRNAs) packaged within, are ideal sources of renal damage markers. In 695 cases, interphase FISH was performed because of no metaphases on direct preparations. Volf: None. Soltysova: None. S.M. Bello: None. Pang, Joyce Lee, Ernest Lam, Mark Oldakowski, Alka Chaubey Bionano Genomics, San Diego, CA, USA. Neurological, psychiatric, electrophysiological, biochemical and genetic tests were performed. We conclude that DEGs in Tcells are mostly involved in ubiquitination and signalling in the immune system. F.B. Belen: None. There was a significant increased risk of CRC development in mutation carriers. Preimplantaion genetic diagnostics (PGD) is a useful approach for reducing miscarriage and increase successful pregnancy rate in couples, carriers of balanced structural rearrangements. Silva: None. The sequencing was performed using an Illumina platform and the sequences were aligned at the reference human genome GRCh38. The median time from GT to RRM was 18.4 months, and from GT to RRSO-10.0 months. Poe: None. Metabolic workup, hearing, abdominal ultrasonography, echocardiography and chromosomal analysis were normal. Biallelic pathogenic variants of the TRAPC11 gene have rarely been associated with various phenotypes from limb-girdle muscular dystrophy (LGMD) to congenital disorder of glycosylation (CDG), associated to various extramuscular symptoms. Subsequently a 3,195 kb duplication was identified at 2q14.3. Two genes associated with autosomal dominant disorders, PROC (OMIM*612283) and HS6ST1 (OMIM*604846) are localized within the duplicated region. Results: Overall, 50% (133/266) of the studied families were genetically characterized. Although clinical spectrum is too high in this chromosomal aberration, the proband showed a cardiomyopathy not previously reported. Thus, the Lithuanian population, as an object of study, is interesting due to its partial isolation with genetic distinctiveness within the European context and with preserved ancient genetic composition. Congenital malformations: 5/9 had heart disease, 2/9 genitourinary anomalies and 6/9 digital anomalies (2 polydactyly). Although there was a benign medical history, this finding led to retrospective re-evaluation of ECGs where consistent aberrations were recognized. J.W.F. Chua: None. This deletion is located in one of the two FERM domains involved in localizing the protein to plasma membrane. Significantly, we have resolved favorably, establishing the diagnosis of the disease in 43% of the cases, the vast majority of them with pediatric neurological rare syndromes. Analysis of CTCF binding allowed to purpose a DFNB1 3D looping model. D.O. Palenzuela: None. Gomez-Carmona: None. Other mutations in NBAS gene have been reported to cause multisystemic disorders with a wide range of phenotypes including recurrent acute liver failure, skeletal dysplasia, eyes pathologies and immunological abnormalities. Dulioust: None. For example, a splicing event of MAN2C1 has a causal effect on breast cancer risk only in breast tissue. Rescheneder: A. Tarasenko 1,2, Nadezda P. This study was funded by the Ministry of Science and Higher Education of the Russian Federation #0852-2020-0028 I. All of these mutations are known being associated to HCM. van der Sluijs: None. Harvey: None. Employment (full or part-time); Significant; Blueprint Genetics, a Quest Diagnostics Company. Relvas: None. This study was supported by basic research project №0546-2019-0002. Mantri: None. Current genetic risk scores (GRS) for CAD predict CAD independent from traditional risk factors, however these scores may not capture all genetically pre-determined risk. Drug doses were determined by MTT assay. P17.033.D New RD-Connect GPAP features implemented in collaboration with Solve-RD, EJP-RD and ELIXIR enable the diagnosis of rare disease patients with previously negative WES/WGS Leslie Matalonga 1, Davide Piscia1, Anastasios Papakonstantinou1, Carles Hernández-Ferrer1, Alberto Corvò1, Steven Laurie1, Carles Garcia-Linares1, Raul Tonda1, Ida Paramonov1, Daniel Picó1, Marcos Fernandez-Callejo1, Dylan Spalding2, Thomas Keane3, Hanns Lochmuller4, Rita Horvath5, Holm Graessner6, Alexander Hoischen7, Ivo Gut1, Sergi Beltran1 1CNAG-CRG, Centre for Genomic Regulation (CRG), The Barcelona Institute of Science and Technology, Barcelona, Spain, 2European Molecular Biology Laboratory, European Bioinformatics Institute, Wellcome Genome Campus, Hinxton, Cambridge, UK., Cambridge, United Kingdom, 3European Bioinformatics Institute, Wellcome Genome Campus, Hinxton CB10 1SD, UK, Cambridge, United Kingdom, 4Children's Hospital of Eastern Ontario Research Institute; Division of Neurology, Department of Medicine, the Ottawa Hospital; and Brain and Mind Research Institute, University of Ottawa, Ottawa, Canada., Ottawa, ON, Canada, 5Department of Clinical Neuroscience, University of Cambridge, Cambridge, UK., Cambridge, United Kingdom, 6Institute for Medical Genetics and Applied Genomics, University of Tübingen, Tübingen, Germany, Tübingen, Germany, 7Department of Human Genetics, Radboud University Medical Center, Nijmegen, the Netherlands, Nijmegen, Netherlands. Pennings1, M. The protocol and the request for waiver of written informed consent, or waiver of IC at all, when not possible, were submitted to the local research ethic committees and informed to the institutional biobanks. The proposed topological model improves our understanding of the mechanisms of deletion formation in the human mitochondrial genome and opens a possibility to predict deletion burden in different human haplogroups and mammalian species. Nevertheless, only the patient carrying the MYBPC3 splicing mutation showed clinical evidence of structural cardiomyopathy. Elze: None. P19.052.D Longer telomeres are not a positive indicator of extreme longevity (95 years and above) in long-lived individuals Maja Šetinc, eljka Celinćak, Luka Bočkor, Nina Smolej Narančić, Tatjana karić-Jurić Institute for Anthropological Research, Zagreb, Croatia. Genetic counselling at an early gestational age is essential, and follow-up ultrasonography should be performed to predict fetal involvement if possible.Funding: Ida Vogel is funded by a research grant from the Novo Nordic Foundation: NNF16OC0018772 S.H. Thomsen: None. However, it will not explain those that act on regulatory processes downstream of transcription. M.J. Pieters: None. Pottinger: None. Sarper: None. Danis: None. N.A. Kozlov: None. Candidate variants were screened in unrelated cohorts of 508 cases, 300 controls and fifteen families (with 51 affected and 47 normal individuals) of Pakistani origin. Mainly, we identified recurrent de novo pathogenic sequence variants in clinically relevant SHANK3, GRIN1 and NSD1 genes, novel de novo pathogenic variants in KDM1A, KMT2E and GNAI1 genes, and a pathogenic sequence variant in EDA gene of maternal origin. Fajkusová: None. A child's coarse facial features, hearing difficulties, recurrent infections, skeletal abnormalities, affected motor skills and intellectual disability should prompt the physician to investigate the possibility of a lysosomal storage disease, including alpha-mannosidosis. Ordered logistic regression of clinical WHO grading on age, stratified by gender, was used to obtain a binary phenotypic classification. The aim of this study was to report the interaction of hsa-miR-122-5p and its target genes in human male testes with SCOS. Additional features can include hearing loss, other cranial nerve dysfunctions, motor, orofacial, musculoskeletal, neurodevelopmental and behavioral complications. Results: Our results confirmed that this TFAP2B deletion affects RNA splicing, and results in loss of exon 4, leading to the appearance of a premature stop codon. Genetic screening of other patients revealed several VUS below 1% in the European population, that could be the single cause for erythrocytosis or could have a combine effect. This diagnostic test evaluated 3 genes - ACTB, ACTG1 and ANKRD11. Strippoli: None. An accurate diagnosis is important to optimise patient management. Mazzà: None. Osteoarthritis is a prevalent joint disease and a major cause of disability worldwide. Suszynska: None. Overall satisfaction with report length was high (79%), yet only 50% were satisfied with the level of detail provided. Results: We have focused on the presence of pathogenic variants in AD-related genes, namely APOE, PSEN1, PSEN2, MAPT, APP and TREM2. VUS were reported only when further studies to confirm the pathogenicity were possible. Becher: None. Introduction: GNAS, located on 20q13.2, is a highly complex imprinted locus from which at least four transcripts (NESP55, GNAS, XL-GNAS and A/B) are generated and, some of them, in an allele specific way. The diagnosis of auditory neuropathy was mainly based on the discordance of electrophysiological tests with acoustic otoemissions present (78%) and brainstem auditory evoked responses absent or desynchronized (81%). Tsiakas: None. Methods: We conducted a one-stage GWAS of CNVs in 839 sepsis cases from the Gen-Sep Network and 1453 controls genotyped with the Axiom Genome-Wide CEU 1 Array (Thermo Fisher Scientific). Thorisdottir: None. Nagy: None. However, modification of DNA sequences can lead to a sub-optimal methylation profile due to technical biases. Based on these results, we encourage standard genetic testing after counseling by a clinical geneticist. Introduction: Genetic testing in patients with suspected hereditary kidney disease may not reveal the genetic cause for the disorder as potentially pathogenic variants can reside in genes that are not known to be involved in kidney disease. One of the dysfunctions in hEDS patients' cells is the impaired transport of extracellular matrix proteins from cells to intercellular space. The library was prepared using enrichment by hybridizationwith NimbleGen probes (Roche). Distribution of genotypes and allelic variants/genotypes was analyzed using the χ^2 test. Viejo-LLorente: None. The ERN-GENTURIS/SOLVE-RD project, re-analyzed exomes from 293 unsolved TRS-cases: adenomatous polyposis (AP; n = 105), hyperplastic polyposis (HP; n = 98), hereditary gastric cancer (HGC; n = 83) and hereditary colorectal cancer (hCRC; n = 7). Donovan, John E. Amoroso: None. Martinelli Boneschi: None. For SNPs, a significance threshold was established at p =3 probands. Afenjar: None. Luleyap: None. Employment (full or part-time); Significant; Centogene GmbH. Supportive care and niacin supplementation resulted in normal ambulation and muscle strength, no respiratory support, complete normalization of metabolic abnormalities and decrease in creatine kinase from 17,000 to 700 U/L. P11.131.A X-linked variants in SHROOM4 are implicated in the formation of VACTERLCaroline M. Introduction: Genetic testing for Cancer Predisposition Syndromes (CPS) is currently offered to patients meeting specific clinical criteria such as age of cancer diagnosis or family history. Conclusion: We provide evidence that different body proportions seen in men and women may contribute to the different risk of CBP between the sexes. Mourot De Rougemont: None. We observed a non-significant but tendentious relationship between ATXN2 intermediate-length repeat expansion and the duplication of the SMN1 gene and ALS. Ortez: None. This group carried out a survey of BSGM members to solicit views on the continuing utility of the guidelines and the changes needed. Colclough: None. Methylation values of eleven out of the 48 tested CRC-associated markers showed a strong correlation (>0.80) with SEPT9. Both cell lines share certain alterations associated with HNSCC, but we also found small regions specifically altered for each line. Recently, Stein et al. The collection of these data enables and facilitates research with cancer cell lines as well as the authentication of the cancer cell lines. P09.029.B RNA sequencing profiling in prefrontal brain cortex ofC9ALS/FTD Maria Isabel Alvarez 1, Francisco Garcia-Garcia2, Rubén Grillo-Risco2, Marta Gracia1, Laia Rodriguez-Revenga1 1Hospital Clinic of Barcelona, Barcelona, Spain, 2Centro de investigación Principe Felipe, Valencia, Spain. Smirnov: None. Yauy: None. Lampreia: None. Results show RRI of PCG requires development of common language between experts, and alignment between their motivations, practices, evaluation criteria etc. Functional in vitro studies are also currently being carried out to clarify the involvement of these new genes in ovarian carcinogenesis. E.Y. Chelysheva: None. Introduction: The MYH7 c.5135G>A p.(Arg1712Gln) variant has been identified in several hypertrophic cardiomyopathy (HCM) patients worldwide and it is classified as likely pathogenic on ClinVar. The attention is paid to the identification of genetic variation, which increases susceptibility because it could help to develop screening strategies and clinical management. Additional analyses are ongoing for various PRS distribution bins, age at onset, the impact of lipid-lowering medication use, and integration of PRS with clinical risk prediction. We hereby report a family with six affected offspring's with CACUT. ELISA was used for detection of IgG to CMV and EBV. Methods and Results: The proband is a young man (32-year-old) who suddenly died during physical exercise. Introduction: Familial hypercholesterolemia (FH) is an autosomal dominant disorder associated with elevated levels of low density lipoprotein cholesterol, leading to increased risk of cardiovascular disease. We hypothesized, that a seven-week treatment with a synbiotic dietary supplement, as compared to a placebo treatment, will increase diversity of the gut microbiome in human participants. Joeri van der Velde, Dennis Hendriksen, Bart Charbon, Mariska K. Van Opstal: None. Clinical diagnosis: Multiple epiphyseal dysplasia (Fairbank type). Clinical exam revealed large anterior fontanelle 4x6cm and blue sclerae. Gln541His) retained more than 80% activity compared to the WT-HNF1α. Aberrant number of copies of specific genes or genomic regions are known to cause pathogenic conditions. Conclusions: The SEMs approach can add information at the level of epigenetic evaluation in the context of MPM. Meiner: None. We performed an erythrokeratodermia panel and then a clinical exome. A thematic synthesis was undertaken to identify major analytical themes. Methods: We used 6447 exome-sequences of healthy, genetically unrelated Europeans of two distinct ancestries (Dutch and Estonian), and calculated the at-risk couples (ARCs) rates for 1929 AR genes. She started with pain in the left gluteal region associated with nodular lesion in the place with progressive growth. R.A. Callus: None. Introduction: Venous Thromboembolism (VTE) is one of the leading causes of maternal mortality. Zguro: None. Corvaja: None. Familial analysis revealed a close relatedness between the two individuals and the identification of additional members of the family compatible with GRNG. The purpose of this project is to evaluate the transcriptomic consequences of 7q11.23 patient-derived iPSC lines and derivatives. Herranz-Cecilia1, A. Materials and methods: A total of 4,291 Hispanic/Latino and 1,657 African American subjects were analysed. Groenner Penna: A. Two were sporadic and caused by a missense change (c.1652A>G; p.(Asp551Gly)) and a 39-kb deletion encompassing TLK2, and one was familial with three affected siblings who inherited a nonsense change from an affected mother (c.1423G>T; p.(Glu475Ter)). Up to 90% of FAP cases are caused by inactivating mutations in APC, and mosaicism has been previously reported in 20% of sporadic cases. Further validations are needed in order to consolidate and refine the model which now has a prediction capacity of about 65%-70% and could be useful for personalised adjuvant therapy. Zucca: A. Materials and Methods: A retrospective review of 15,836 referred cases over a period of 28 years (1992-2020) were diagnosed with standard karyotyping analysis for constitutional chromosomal abnormalities at Cytogenetics laboratory, Department of Pathology and Laboratory medicine at King Abdulaziz Medical City, Ministry of National Guard - Health Affairs, Riyadh. Single nucleotide variants within known disease-causing genes and copy number variants were classified according to ACMG guidelines, the ACGS Best Practice Guidelines and consensus opinion. Babushkina, Anton V. Also, XPG-His/His genotypes had 1.2-fold increased risk of BC in younger BC patients(A) and the father (TH:c.614T>C). Castillejo: None. S.L.V.M. Stroeks: None. In addition, these studies proposed about 20 genes of interest such as DOCK1 and FGFR2 to explain the different clinical features observed. During the paroxysmal episodes the most common symptoms were: hypotonia (82.4%), symptoms including the orofacial area (85.3% i.a. dysarthria, dysphagia, mutism), ataxia (76.5%) and cognitive decline (61.8%). Each array was consisted of 200k SNP and 550k non-polymorphic markers. Štekrová: None. A chromosomal microarray analysis demonstrated a microduplication of 11,3 Mb on chromosome 2p15-p13.2, containing 99 OMIM genes. Employment (full or part-time); Significant; NIMGenetics. Variant calling and interpretation of pathogenicity was performed using the IonReporter v.5.14 variant analysis software and the ACMG criteria. Mean time between order and validation of an assay was 14 days. Newborn Ifitm5 S42L mice, heterozygous(HET) and homozygous(HMZ), are non-lethal, have flared rib cage, shoulder and knee dislocations. Introduction: Inherited ichthyoses represent a heterogeneous group of skin disorders characterised by impaired epidermal barrier function and disturbed cornification. Results: The NGS-based CNV-analysis revealed a 40 Mb triplication (CN4) on chromosome 9, region 9p:31023-40232529. Materials and Methods: We examined 115 breast carcinomas and 15 cfDNA samples. Atawna3, Gillis David4, Orli Halstuk1, Nava Shaul-Lotan1, Mordechai Slae4, Mutaz Sultan5, Vardiella Meiner1, Orly Elpeleg1, Tamar Harel1 1Department of Genetics, Hadassah-Hebrew University Medical Center, jerusalem, Israel, 2Department of Pediatrics, Makassed Hospital and Faculty of Medicine, Al-Quds University, East Jerusalem, Israel, 3Department of Neonatology, Makassed Hospital, East jerusalem, Israel, 4Department of Pediatrics, Hadassah-Hebrew University Medical Center, jerusalem, Israel, 5Department of Pediatrics, Makassed Hospital and Faculty of Medicine, Al-Quds University, East jerusalem, Israel. Ozer: None. Aparicio: None. P08.024.B Development delay in paediatric patient with deletion on chromosome 15q26.2 Milica Pesevska 1, Violeta Anastasovska1, Elena Sukarova-Angelovska1, Dragica Nestoroska1, Gordana Ilieva1, Sandra Panovska2 1Genetic Laboratory, University Clinic for Pediatrics, Ss.Cyril and Methodius University in Skopje, Faculty of Medicine, Skopje, Macedonia, The Former Yugoslav Republic of, 2Department of Human Genetics, Avicena Diagnostic, Skopje, Skopje, Macedonia, The Former Yugoslav Republic of. Features also included ophthalmologic abnormalities, hearing impairment, and EEG anomalies. de Leeuw1, Thirsa Kraaijenbrink1, Yoan Diekmann6, Manfred Kayser2, Mark G. Quantitative DNA methylation analysis of the bisulfite-treated DNA was performed by pyrosequencing on a PyroMark Q24 (Qiagen, Germany). Raynova: None. P15.012.D Implementation barriers of dynamic consent in clinical genetics Tita Alissa Bach, Sharmini Alagaratnam, Serena Elizabeth Marshall DNV GL, Oslo, Norway. These results will be helpful to increase the knowledge of predisposition to early-onset gastric cancer. Acknowledgements: This research was supported by the Science Fund of the Republic of Serbia, PROMIS, # 6066923, miFaDriCa, and Serbian Ministry of Education, Science and Technological development. P4H-TM wild type and variant constructs without the transmembrane region were overexpressed in insect cells and analyzed with SDS-PAGE and Western blot. CA-HIV-1 DNA and CA-HIV-1 RNA levels were measured with droplet digital PCR assays and genotype information (522,455 SNPs) was retrieved via Infinium Global Screening array platforms. Haberman: None. Escudeiro: None. Lupski4,11,12,8, Ben Odermatt2, Heiko Reutter3, Gabriel C. OOC patients US, United States; B.C., British Columbia; UK, United Kingdom NCCN, Overall In criteria Out of criteria Country/providence Guideline Total n of cohort IC (% of total cohort) OOC (% of total cohort) Total PV IC (% of IC cohort) Total PV OOC (% of OOC cohort) High risk^ PVs (% of total PVs) High risk^ PVs (% of total PVs) U.S. NCCN 953 473 (49.6) 480 (50.4) 43 (9.1) 40 (8.3) 22 (26.5) 8 (9.6) Ontario MOHLTC 953 210 (22.0) 743 (78.0) 18 (8.6) 65 (8.7) 5 (6.0) 25 (30.1) B.C. BCHCP 953 203 (21.3) 750 (78.7) 24 (11.8) 59 (7.9) 9 (10.8) 19 (22.9) Australia eviQ 953 180 (18.9) 773 (81.1) 19 (10.6) 64 (8.3) 12 (14.5) 18 (21.7) U.K. NICE* 826** 127 (14.7) 736 (85.3) 11 (8.7) 64 (8.7) 6 (7.2) 22 (26.5) S.M. Nielsen: A. Mild forms of HPP are more frequent than severe forms - expected prevalence can reach 1/6000 in Western populations. Materials and Methods: We performed a NGS custom panel containing 1663 genes involved in common genetic disorders (RD seq (R) v6.0), and a karyotype using G- and C-banding techniques. We did not find evidence of a causal association between higher BMI and lower levels of vigorous physical activity (P = 0.11) or moderate physical activity (P = 0.25). However, increased prevalence was observed in patients with certain rare diseases (King et al. We summarised phenotype frequencies per gene, comparing patterns across genes. The initiative was supported by an unrestricted grant from Novo Nordisk Europe A/S. The Blast tool was used to align the resulting sequences with those reported in the GenBank. He has severe psychomotor delay, behavior abnormalities, failure to thrive (at 14-months was placed with percutaneous endoscopic gastrostomy), epilepsy and recurrent infections. Materials and Methods: The clinical validation was performed on 842 whole blood samples in total, 184 for Factor II, 186 for Factor V, 111 for Factor XIII, 123 for MTHFR A1298C, 123 for MTHFR C677T and 115 for PAI-1. We need to unravel the molecular bases underlying these Mendelian disorders whose molecular causes escape to the prevailing techniques because there are a notable proportion of patients who remain without diagnosis. Material and Methods: Tumor-normal sequencing was performed in 578 gynecological, skin and gastrointestinal cancer patients without previous genetic diagnosis between 01/2019-01/2021. J.A.L. MacArthur: None. Whole genome sequencing (WGS) was subsequently pursued on two individuals. The mutation analysis was performed using targeted next generation sequencing. Chromatin immunoprecipitation analyses demonstrate enrichment of a large network of keys transcription factors (TFs) in intestinal cells, such HNF1a, p300, FOXA1/A2, CDX2 and TCF4, in introns 24 and 26 enhancers.In conclusion, two new CREs with cooperative enhancer activities have been identified, enriched with important TFs, redefining the 3D regulation model of the CFTR gene in intestinal cells. Pathogenic hemizygous MECP2 variants in males are usually embryonic lethal or cause severe neonatal encephalopathy. Materials and Methods: We examined 27 unrelated probands with a clinical diagnosis of HME using mass parallel - massive for all EXT1 and EXT2 coding regions, followed by validation of the results by Sanger sequencing. Stepanov1 1Research Institute of Medical Genetics, Tomsk National Research Medical Center, Tomsk, Russian Federation, 2Institute of Ecological Medicine, Daghestan State Medical University, Makhachkala, Russian Federation, 3Institute of Physics, Daghestan Federal Research Center, Makhachkala, Russian Federation. In the leukocytes of patients with CAD, the methylation level of CpG sites in the analyzed region of MPO (chr17:56356470, GRCh3 [hg19]) on average was significantly lower (26.5% [24.5%; 32.3%]) than that in the control group (35.4% [30.3%; 42.6%], $p = 3.83 \times 10^{-7}$). Funding: Regional Government of Castilla-and-Leon to the University of Valladolid (Spain). The identified DEGs in SYS fibroblasts suggest a potential novel role for MAGEL2 in mitosis and extracellular matrix homeostasis that should be further studied.Funding: Associació Síndrome Opitz C, Spain; Spanish Government (CIBERER -U720; PID2019-107188RB-C21, SAF2016-75948-R, FECYT-PRECIPITA); Catalan Government (PERIS SLT002/16/00174). Employment (full or part-time); Significant; Sofiva Genomics Co., Ltd. We performed exome sequencing (ES) and cDNA sequencing of the targeted MYH3 region. Additionally, OGM provides extra relevant information, such as the 4qA or 4qB haplotype and SMCHD1 structural variations. Sharma: None. Patients and methods: 24 patients with Pompe disease were enrolled. Bézieau: None. We found the highest activity between 24-30 bp long gRNAs with limited mismatch tolerance. Pospelova: None. We performed phenotype and genotype analysis, critical region delineation and assessment of the impact of structural variants on three-dimensional chromatin interactions by Topologically Associating Domains (TADs) analysis. Leitch: None. de Boer*3,4, A Jackson*5, E Benetti*6, S Banka5,7, G Casari8,9, A Ciolfi10, J Clayton-Smith5,7, B Dallapiccola10, K Ellwanger11,12, L Faivre2,13, C Gilissen3,14, H Graessner11,12, T B. Gotovtseva: None. Novelli: None. Institut d'Investigació i Innovació Parc Taulí I3PT. The variables most associated with diagnosis were: diagnostic orientation in the referral (p = 0.001), multiple congenital anomalies (MCA) (p G p.(Tyr179Cys) c.734G>A p.(Arg245His) ˃10 adenomas (44) right-sided (43) bifocal breast cancer (44) MGF:rectal (65) / 2. Materials and Methods: Primary human coronary- (HCAEC) and internal thoracic artery endothelial cells (HITAEC) exposed to 500 ng/ml MMC (experimental group) and nonexposed control were used in this research. Trebušak Podkrajšek: D. The logic behind this finding was that long lived and slow-dividing cells have a rich aerobic environment, permitting a high oxidative metabolism, while short-lived fastly-dividing cells can run out of oxygen ending up in hypoxic conditions. Material and Methods: We investigated a French family including 2 patients presenting an IPPSD2 phenotype. M.G. Thomas: None. Preliminary follow-up studies replicated the ApoE variant in external datasets. van Ravenswaaij-Arts1, Wilhelmina S. Results: There were found a significant correlation of the TNF-α gene variants (308A-allele) and duration of intubations on lung mechanical ventilation (r = 0.967, p = 0.0001). However, we are collecting WES data to re-analyse these cases. Karczewsk3,4, Brian Cole5, Bao-Li Loza6, Sander W. This project should allow us to better understand the role of autoimmunity in PD and to identify new biomarkers. Nevertheless, use of the DeSIRe by HCPs in the PTPP to support decision-making about cascade screening is feasible and acceptable. We are reporting BCL11B variant as a de novo mutation as it has been reported previously in other studies. J.M. Ellingford: None. Copy number variant analysis from exome data, identified a homozygous intragenic non in-frame deletion of 1.84 Kb encompassing exons 8 and 9 of YY1AP1 confirming a molecular diagnosis of GRNG. Introduction: Pharmacogenomic tests are available to guide treatment. Although effect size is small and has no diagnostic significance, understanding the mechanism underlying this association may lead to identification of new targets for therapeutics development. SHFM3 (10q24) displays dominant inheritance. P09.134.C 90% TSC1/TSC2 mutation detection rate in Tuberous Sclerosis Complex patients without mutation identified in commercial laboratories Katarzyna Klonowska 1, Joannes Grevelink2, Krinio Giannikou1, Magdalena Tyburczy1, David Kwiatkowski1 1Brigham and Women's Hospital/Harvard Medical School, Boston, MA, USA, 2Boston Dermatology and Laser Center, Massachusetts General Hospital, Boston, MA, USA. We also measured expression of Padi genes and various inflammatory cytokines in immune cells by real-time TaqMan assay and ELISA, respectively. Results: We demonstrated that mean of the number of total SEMs (hypo and hyper) was higher in cases respect to controls. Iasevoli: None. This suggests that the divergence in phenotype of patients with this syndrome is not related to the type of mutations identified, but is more likely a result of additional genetic or epigenetic factors. Materials and Methods: Two siblings with similar findings who were being followed up in the pediatric neurology clinic due to loss of speech, cognitive and motor development retardation were consulted for genetic evaluation. Currently, variant penetrance data predominantly comes from small disease cohorts and biased case studies. Rohde: None. Batty: None. Out of 31 hospitalized patients, 6 patients died of complications caused by COVID-19. ArrayCGH analysis allowed to confirm the presence of a 5,3 kb deletion encompassing exons 2 and 3 of the gene: arr[GRCh37]6q14.1(76515168x2,76527247_76532572x1,76537323x2). This study aims to determine the diagnostic yield of whole-exome sequencing (WES) for monogenic diseases and to identify phenotypes associated with a genetic etiology. Zanoaga: None. Szeinberg: None. In F9 intron 6 (c.727+1853_1854ins), we identified the insertion of a 1.377 kb processed pseudogene (retrocopy) of HNRPNC transcript (NM_004500.6) lacking the end of the 3'UTR, in opposite orientation to the F9. Coats' disease (OMIM300216) is a form of retinal dystrophy which occurs due to congenital abnormality of retinal vessels. Bosch: None. The region contains several autosomal dominant transmission genes: GJB3, KCNQ4 associated with neurosensory deafness, COL9A2 - epiphyseal dysplasia, COL8A2 - corneal dystrophy/ aortic malformations, SLC2A1 - Dystonia/epilepsy. Ugarov: None. We wanted to expand our knowledge about the phenotypes associated with genes linked to seizures. We generated PADI4−/− and PADI2−/− mice and performed experimental arthritis. Y.B. Lebedev: None. Results: We observed that using the automated workflow, the LoD is 1 copy/uL for SARS-CoV-2 with a mean Ct 36. This with two sub-questions: do they have common characteristics that would allow a genetic counseling in prenatal context and why do large CNV without phenotypic consequence in a parent is expressed in his offspring? Birk: None. Analysis of cDNA indicated that exon 5 (84bp) was skipped, and was replaced by 93bp of retained intronic sequence, preserving the reading frame yet altering a significant number of residues. P18.017.C A molecular approach to precision medicine in South African children with epilepsy: towards a genetics-based diagnostic service for epilepsy in childhood Caitlin Mary McIntosh 1, Karen Fieggen1, Jo M. Kunz10,11, Alexandre Reymond12, Ilia Mazunin13,14, Georgii A. For these cohorts, the first short-read genomes are being performed. T/C-C/C, OR = 1.91; p = 0.031), it was found that rs2074192 and rs5186 showed a protector effect (G/C vs. P01.058.B Neurofibromatosis type 1 and the next generation: is preimplantation genetic testing the solution? Koev: None. Chew, L H. We accompany our method with a fully interactive web app allowing exploration, visualisation and validation of phenome-wide mantis-ml predictions. van Langen1, Imke Christiaans 1 1University Medical Center Groningen, Groningen, Netherlands, 2University Medical Center Groningen;, Groningen;, Netherlands, 3University Medical Center Utrecht, Utrecht, Netherlands, 4Amsterdam University Medical Centers, Amsterdam, Netherlands. An additional rare MYH11 variant may account for the brain infarctions in this child. Results: Skeletal survey showed brachydactyly and cone-shaped epiphyses of phalanges, corroborating the clinical suspicion of TRPS1. Introduction: Discovered in 2019, the novel Coronavirus can infect human and causes acute respiratory syndrome (SARS-CoV-2) infection has spread to more than 200 countries, causing thousands of deaths. Aneuploidies were revealed with higher frequency in the karyotyped compared to the FISH-analyzed group: 73.4%(1332/1814) vs 63.8% (256/401) (p = 0.0001). P12.194.B Exploring Transposon Activity in Hematological Malignances Anastasiya Volakhava, Sarka Pavlova, Marcela Krzyzankova, Karol Pal, Hana Synackova, Alexander Komkov, Sarka Pospisilova, Ilgar Mamedov, Karla Plevova CEITEC, Brno, Czech Republic. Z.G. Yan: None. Bezzina Wettinger: None. Turnbull: None. Support: The National Science Centre grant no.2018/31/B/NZ5/03280. Results: Thirty-five patients (70%) carried IC2-LoM, 11 (22%) chromosome 11 paternal uniparental disomy (UPD(11)pat), 1 (2%) Imprinting Center 1 Gain-of-Methylation (IC1-GoM); 2 (4%) tested negative and 1 (2%) refused testing (the latter were clinically diagnosed with BWSp score ≥ 4). Kurtis: None. Mutational burden analysis comparing the frequency of predicted pathogenic variants in cases vs. Compared to individual-level genetic data, GWAS summary-level data are easier to acquire and computationally more tractable even for very large sample sizes. P20.020.C Maternal-effect variants in PADI6 and NLRP2 genes associated with reproductive anomalies, Multilocus Imprinting Disorders (MLID) and Beckwith-Wiedemann syndrome (BWS) Pierpaola Tannorella 1, Luciano Calzari1, Alessandro Vimercati1, Ester Mainini1, Davide Gentilini2,3, Maria Teresa Bonati4, Cecilia Daolio5, Annalisa Pedrolli6, Lidia Larizza1, Silvia Russo1 1Istituto Auxologico Italiano, IRCCS, Cytogenetics and Molecular Genetics Laboratory, Milano, Italy, 2Istituto Auxologico Italiano, IRCCS, Molecular Biology Laboratory, Unit of Bioinformatic and Statistical Genomic, Milano, Italy, 3Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy, 4Istituto Auxologico Italiano, IRCCS, Service of Medical Genetics, Milano, Italy, 5Pediatric Unit, Carlo Poma Hospital, Mantova, Italy, 6IDivision of Pediatrics, S. In 26 out of 30 patients an initial diagnosis was presumed; in 14 cases the molecular findings coincided and in 12 they did not. Introduction: Hearing loss is one of the most prevalent disabilities worldwide. Sansone: None. A higher number of methylated CpGs was found in shores and shelves compared to CpG islands, compatible with the role of those genomic regions in gene regulation. Samples of 250 breast cancer patients and 250 age and gender matched controls were genotyped for VEGF -2578C/A, -2549I/D, -460T/C, +405C/G, -7C/T and +936C/T polymorphisms. The majority of them are localized in the MYO15A (n = 6) and PAX3 (n = 5) genes. Recently, exome survey and large-scale re-sequencing confirmed TRAP1 and ZIC3 as VATER/VACTERL disease genes. G.A. Kuchel: None. J.M. Fatih: None. SMS satisfaction questionnaires sent to patients. To date, five genes (NIPBL, SMC1A, SMC3, RAD21 and HDAC8) have been associated with CdLS. The average week of gestation at the time of positive prenatal diagnostics decreased significantly for both anomalies (P C, did not show impact according to splicing predictors. We conducted whole-exome sequencing in a 9-year-old Lebanese girl with a CD onset at 13 months and in both her asymptomatic parents. T.I.A. Sørensen: None. Grant/Award Number: FWOTBM2018000102 L. Results: The published variants showed poor co-segregation with diabetes (combined LOD scores: BLK 1.16, KLF11 1.2, PAX4 7,000 estimated) and their genetic heterogeneity make the identification of existing treatments difficult for clinicians. The data was then processed using several pipelines (structural variant, variant calling, copy number variant). Acknowledgements: C.V. is supported by BONFOR grant O-149.0133. Conclusions: Our data shows that DNA methylation is involved in HSCR pathogenesis, and suggests the involvement of MAB21L2 in disease development. van Koolwijk2, Frans van Agt2, Yvonne H. He also presents microcephaly, facial dysmorphism, strabismus and fifth digits with bilateral hypoplastic distal phalanges. We performed principal component analysis (PCA), as well as hierarchical and non hierarchical clustering. Results: POLG variant rs3087374 was significantly associated with tumor pathomorphological parameters. on the space of surnames or of migrations. Goldgar: None. The second SSC took a more in-depth view of genetics and focussed on the challenges of communicating genetic information. A better understanding of the biology underlying variability in plaque composition will provide insights into the progression of cardiovascular diseases. Tsafantakis: None. Improved model designs will leverage select mouse genetic tools and strains in the context of age, gender or comorbidities to replicate pulmonary, immunopathological or systemic hallmarks of severe COVID-19 and explore genetic/other modifiers of susceptibility, progression and outcome. Contrarily, the annotation of the genome is incomplete, and the data is scattered along different databases, making SV manual evaluation almost impossible. Bichev: None. NGS panel of genes involved in skeletal dysplasias found an heterozygous variant (c.5285G>A) in FBN1 gene in both father and daughter, previously unreported; a different pathogenetic variant involving Glycine 1762 has been associated with both Acromicric and Geleophysical dysplasia. In our cohort WES was performed on 128 fetus -parents TRIOs with fetal structural anomalies in ongoing pregnancies and normal karyotype and CNV analysis. Pegoraro: None. Whether this is due to ART or confounding effects of advanced parental age was unknown. Marjonen: None. P15.007.C Automation of NGS library preparation for hybrid capture Zachary Smith Beckman Coulter Life Sciences, Indianapolis, IN, USA. Gharyani Fétoui: None. The other three families did not reveal suggestive linkage. The patient presented with dysmorphic features, neonatal hypotonia, severe neurodevelopmental and speech delay, as well as, Lennox-Gastaut seizures, scoliosis, hip dysplasia, and joint hypermobility. Collapsing analysis compares the number of rare variants in each gene between cases and controls, to detect genes in which rare variants are significantly enriched or depleted for a given phenotype. S.A. Loutfy: None. Salvadores: None. Camanni: None. Marusin 1, Alexander N. Depauw: None. Muru: None. Material and methods: Biochemical determination of protein levels and activity were carried out. Defects in the planar cell polarity (PCP) and the folates metabolism pathway have been strongly associated with NTDs in animal models and recent studies of human cohorts. M.C. Martínez-Romero: None. Maniere: None. Klaschka: B. Rader: None. P11.032.B Diagnostic WES-based gene panel testing in (non)-syndromic patients with cleft lip and/or palate in the NetherlandsInge L. Serrano-Antón1,2,4, M J. P14.011.D Down syndrome with an inherited translocation t(6;21)(q13;q22) Rawia Kammoun 1, Imene Boujelbene1, Ikhlas Ben Ayed1, Nourhene Gharbi1, Mohamed Ali Ksentini1, Ines Ouertani2, Fatma Abdelhedi1, Hassen Kamoun1 1Medical Genetics Department, Hedi Chaker Hospital, sfax, Tunisia, 2Department of Congenital and Inherited Disorders,Charles Nicolle Hospital, Tunis, Tunisia. Ravnik-Glavač: None. Furthermore, cancers as well as cancer cell lines exhibit copy number variation (CNV) profiles that show regions in the chromosomes that have been deleted or amplified. Hoffmann-La Roche, PharmaMar, Millenium Pharmaceuticals, Clovis Oncology, Astra Zeneca NV, Tesaro, Oncoinvent AS, Immunogen, Sotio. Büttner: None. Conclusions: These data demonstrate the predictive accuracy of FMP in NaV1.1 in identifying specific functional domains apparently intolerant to genetic variability, establishing its utility in supporting clinical variant interpretation in germline genetic testing. 2) Low-grade mosaicism of de-novo mutations may be missed in trio-exome sequencing approaches, which should carefully be taken into account. Introduction: Here we report a case of mosaic trisomy 7 diagnosed incidentally, by the prenatal screening of cfDNA (CentoNIPT®) in a31 years old pregnant women resulted inconclusive for trisomy 21, 18, and 13 at 15 weeks of gestation. Four subjects homozygotes or compound heterozygous for a class I-II mutations of CFTR gene and with MTHFR CC genotypes had a less severe phenotypic expression with milder lung inflammation without pancreatic insufficiency. Otero-Rodríguez: None. Prenatal lymphatic problems most often presented as an increased nuchal translucency and/or chylothorax. Piechota: None. The inheritance of human traits is usually divided into two major classes, monogenic and polygenic or complex. Polak2, Karin E. We assessed credibility of pooled associations using interim Venice criteria. Jansová: None. Specchio: None. For quantification of HRD a LOH-score based on Swisher et al (2017; PMID: 27908594) and an Aneuploidy Normalized Telomeric Imbalance-Score (ANTI-Score, unpublished) were defined. Five patients had attention deficit and/or hyperactivity. The rare variants shared by at least 2 unrelated patients were selected, including truncating, splicing and missense variants from a list of known or suspected genes involved in oncogenesis. We present the case of a fetus of consanguineous parents with ultrasound anomalies and normal CMA result, where WES uncovered two distinct pathogenic variants. I.Z.M. Eltazi: None. Vaiteniene: None. The aim of this study is to calculate the estimated prevalence of NPC in Quebec to determine if it is underdiagnosed in the population. Kavakli: None. UMOG is a multidisciplinary diagnosis and research team with extensive experience in diagnosis, research and teaching in ophthalmogenetic diseases in Hospital La Paz (Madrid). van Langen: None. In addition, NGS revealed a new frameshift deletion in exon 19 of the TBK1 gene (I669Sfs*). Pace1, Dillon Mintoff2, Peter Bauer3, Isabella Borg 1,2 1University of Malta, Msida, Malta, 2Mater dei Hospital, Msida, Malta, 3Centogene GmbH, Rostock, Germany. After performing a-CGH, 28 cases had solo and 60 trio ES. Rey: None. The genetic diagnosis was made before or after identifying the glycoform abnormality in this screening. P12.041.A Exploring clonal evolution and genetic causes of therapy failure in chronic lymphocytic leukemia Kristýna Závacká 1,2, Petr Tauš2, Karol Pál2, Kamila Stránská1,2, Šárka Pavlová1,2, Anna Panovská1, Šárka Pospíšilová1,2,3, Karla Plevová1,2,3 1Department of Internal Medicine – Hematology and Oncology, University Hospital Brno & Medical Faculty, Masaryk University, Brno, Czech Republic, 2Center of Molecular Medicine, Central European Institute of Technology, Masaryk University, Brno, Czech Republic, 3Institute of Medical Genetics and Genomics, University Hospital Brno & Masaryk University, Brno, Czech Republic. Materials and Methods: Patients with biallelic pathogenic or likely pathogenic HACE1 variants were identified by trio exome sequencing by the Deciphering Developmental Disorders (DDD) Study or whole genome sequencing by the 100,000 Genomes Project. Prochazka: None. Of the 468 P variants, 150 (32%) resided in the cytoplasmic region, including a C-terminal cluster within the CaM-binding domain (aa 1915-1944), 119 (25.4%) in the transmembrane, 29 (6.2%) in the S4-voltage sensor, 45 (9.7%) in the "pore", and 125 (26.7%) in the extracellular domains. Mirabelli: None. Wand: None. P.R. Dinçer: None. García-Peláez: None. Girl phenotype: dolichocephaly, high forehead, flattening of the middle part of the face, deep-set eyes, full and puffy eyelids, long eyelashes, hypertelorism, full cheeks, enlarged ears. J.B. van Meurs: None. In children with confirmed molecular results, seventeen out of 31 (54,8%) patients showed autosomal recessive inheritance patterns, thirteen out of 31 (41,94%) showed autosomal dominant and one case had X-linked hearing loss. Çevik: None. P23.033.A Definition of personalized medicine: links with familiarity and knowledge in genetics Valentyn Fournier, Loris Schiaratura University of Lille, Villeneuve-d'ascq, France. J.D. Windster: None. The condition has a multifactorial etiology with a strong genetic component. Materials and Methods: We performed Mendelian Randomization using a genetic instrument for age at menopause (ANM) comprised of 290 variants from GWAS in >200,000 women. Case Report/Methods: Proband DGRC0021 presents with a familial apparently balanced t(17;19)(p13.1;p13.3)mat, craniofacial dysmorphisms, global developmental delay and aggressive behavior. In the extracellular microenvironment, auxiliary proteins control cell behavior and coordinate embryo development by acting as co-receptors or direct antagonists of defective bone morphogenetic protein (BMP), Activin and TGF-β ligands. Women had a generally later-onset disease with 14% of female carriers diagnosed with HCM at age 50, compared with 54% of male carriers, and penetrance reaching 95% and 92% at age 70 in men and women, respectively. J.H. Döring: None. Nuclear localisation was not significantly altered in any of examined mutated proteins. The hormonal-lipid cluster grouped 85 SNPs with shared effects on hormone and lipid levels. Logistic-regression analysis was used to assess the association of PRS with PD-status and each risk factor with PD-status. Yaneva-Staykova: None. Biological and radiological investigations were normal. Until recently, there were few studies analysing genomes of individuals that experienced high levels of ionizing radiation at a DNA sequence level. Akhmetova: None. Wiersma: None. Both WGS and gold-standard ATXN2 CAG PCR genotypes are available for all individuals. P11.104.B Spectrum of mutations in Ras-MAPK pathway in Russian probands Anna Orlova, Alexander Polyakov, Polina Gundorova, Oksana Ryzhkova Federal State Budgetary Scientific Institution "Research Centre for Medical Genetics", Moscow, Russian Federation. Encouragingly, additional cases with more severe phenotype have been identified by using GeneMatcher. The prevalence varies from 0,35 to 2,2 per 100000 births depending on the country. Balabanski: None. Introduction: Loeys-Dietz syndrome (LDS) is a systemic connective tissue disorder characterized by vascular findings, skeletal abnormalities, craniofacial features and cutaneous findings which sometimes can be misdiagnosed as Marfan syndrome The diagnosis is established based on clinical findings and the identification of heterozygous pathogenic variant in one of the several reported genes. Saini: None. P11.007.A Interstitial deletion of 2q32.3q33.3: Two case reports of SATB2-Associated-Syndrome and Immune System alterations Joana Adelaide Catanho 1, Ana Isabel Cordeiro2, Teresa Kay1, Inês Carvalho1 1Serviço de Genética Médica, Hospital Dona Estefânia, Centro Hospitalar e Universitário de Lisboa Central, Lisboa, Portugal, 2Unidade de Imunodeficiências Primárias, Hospital Dona Estefânia, Centro Hospitalar e Universitário de Lisboa Central, Lisboa, Portugal. Å. S.K. Abilev: None. Discussion: Based on our study the localization of mutation and protein domain involvement correlated with the GAA activity. A.A. Zarubin: None. M.D. Donadio: None. For the remaining 10 genes, the germline transmission of the mutation failed despite multiple attempts or no mouse model was available during the course of the study. A founder mutation (c.204_214del11; p.Gly69ArgfsX10) has been described in Eastern Europe. A considerable number of gene defects have been shown to cause short stature, but there are only few examples of genetic causes of non-syndromic tall stature. Separating consent for panel analysis and exome-wide analysis might help parents to make a deliberate decision. Among all known genetic causes, loss of function mutation in TCIRG1 gene is responsible for the disease in 70% of the cases. We uniformly assessed all variants for pathogenicity, penetrance, prevalence, and phenotypic and geographic heterogeneity. Introduction: Recent genome-wide association studies (GWAS) identified over 100 alcohol consumption-associated genetic variants. A minimum VAF of 5% was set in aspirates to filter out low frequency variants of normal tissue. P12.134.B Frequency of de novo and mosaic STK11 variants in Peutz-Jeghers syndrome Albain Chansavang 1,2, Marion Dhooge2,3, Aurélie Toussaint1, Véronique Duchossoy1, Virginie Benoit1, Joëlle Cohen1, Chrystelle Colas4, Hélène Delhomelle4, Pierre Laurent-Puig5, Aziz Zaanan6, Solenne Farelly3, Camille Tlemsani2, Romain Coriat3, Audrey Briand-Suleau1,2, Béatrice Parfait1,2, Eric Pasmant1,2, Nadim Hamzaoui1,2 1Service de Génétique et Biologie Moléculaires, Hôpital Cochin, APHP.Centre Université de Paris, Paris, France, 2Institut Cochin, Inserm U1016, CNRS UMR8104, Université de Paris, CARPEM, Paris, France, 3Service de Gastroentérologie et Endoscopie, Hôpital Cochin, APHP.Centre Université de Paris, Paris, France, 4Département de génétique, Institut Curie, Université de Recherche Paris Sciences et Lettres, Paris, France, 5Service de Biochimie, Pharmacologie et Biologie Moléculaire, Hôpital Européen Georges-Pompidou, AP-HP, Université Paris Descartes, Paris, France, 6Service de Gastroentérologie et Oncologie Digestive, Hôpital Européen Georges-Pompidou, AP-HP, Université Paris Descartes, Paris, France. Plumitallo: None. Our report broadens the phenotypic and genetic spectrum of MESD-related OI, provides additional insight into the pathogenic pathways and underscores the necessity of MESD for normal WNT signaling and bone formation. However, the mouse and human bone phenotypes associated with this gene do not fit with HBM. Janus: None. Arnedo: None. All had global developmental delay and learning difficulty. Denguezli: None. Ambrós: None. The aim of this study was to investigate the association between LTF gene single nucleotide polymorphisms in amino acid positions 29 and 47 and dental caries. All those classified as typical met van der Burgt diagnostic criteria compared to 75% of the atypical ones (p = 0.003). In CH, the first-tier screening test is the measurement of methionine by MSMS. Lebedev1 1Scientific Research Institute of Medical Genetics, Tomsk National Research Medical Center, Tomsk, Russian Federation, 2National Research Tomsk State University, Tomsk, Russian Federation. Unlike previous studies, hepatomegaly was a main concern in our patients due to the high prevalence of viral hepatitis while skeletal deformities are not! as childhood rickets is not rare in Egyptian population. Muñoz Esparza: None. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Significant; the French Ministry of Health (DGOS, PREPS-17-0385, 2017). Yılmaz: None. J.S. Ware: None. Results: New variants (T/A-13883, A/C-13921, T/C-13961 and C/A-13962) were detected in the analyzed region in addition to the previously described C/T-13910 and T/G-13915 variants. The study was supported by the Russian Science Foundation (19-74-10026). Khusnutdinova: None. Nedelea1,2,3, Azdasher Naszan4, Danae Stambouli1 1Cytogenomic Medical Laboratory, Bucharest, Romania, 2Filantropia Clinical Hospital, Bucharest, Romania, 3Carol Davila University of Medicine, Bucharest, Romania, 4CF2 Clinical Hospital, Bucharest, Romania. E.S. Luckett: None. Methods: clinical and molecular features of 50 ART-BWSp patients were reviewed. Materials and Methods: Investigation of the role of the variant followed this workflow: in silico analysis of the 5'UTR; study of allele-specific expression in patients derived cells; evaluation of the impact of 5'UTR variant, relative to the WT allele, on LMX1B expression in heterologous cell-based assays. Also, given the known molecular genetic markers, significant for diagnosis, prognosis and monitoring, it is highly recommended to combine karyotyping with molecular genetic analysis. Six patients had heterozygous pathogenic KMT2D variants (five nonsense and one missense variants). The detected variants were evaluated according to the ACMG guideline. We selected 30 patients who underwent WES and in whom (likely) pathogenic CNVs were detected. Conclusions: Two-thirds of patients with early-onset CKD in this cohort had a genetic cause. Riedhammer 1,2, Matthias C. Only two cases of Costello syndrome have been reported with moyamoya disease. We analyzed ES data using a custom in-house research pipeline searching for recessive (homozygous, compound heterozygous), dominant/de novo, and X-linked variants. Bean et al. This can reveal several hearing loss syndromes before involvement of other organs/systems, thus allowing the surveillance of present and/or future complications associated with these syndromes. Barra: None. C.A. Heckman: None. The second patient had hemophilia A, an X-linked recessive condition caused by mutation in F8 gene. Mahdouani: None. We show that patients harboring highly clustered missense variants within the 2nd and 3rd zinc finger domains are not clinically distinguishable from patients with truncating variants. We detected two FMR1 premutation carriers (2.2%), well within the range reported by multiple studies in ataxic cohorts (0-4.1%), and higher than other, movement disorder, cohorts (T:p.(I465F)); 2) a boy with bilateral anophthalmia, developmental and intellectual delay, seizures and autistic features with compound heterozygous variants (c.845G>C:p.(G282A);c.1459A>G:p.(R487G)); 3) a girl with bilateral microphthalmia and coloboma with compound heterozygous variants (c.847_849del;p.(G283del);c.953C>A,:p.(S318Y)); 4) a girl with bilateral anophthalmia with a homozygous missense variant (c.1144G>A:p.(G382R)); 5) a boy with bilateral microphthalmia, unilateral coloboma and cataract, with a homozygous splice variant (c.1233+2T>C) and 6) a boy with bilateral microphthalmia, iris and chorioretinal coloboma, facial dysmorphism with a homozygous missense variant (c.434C>T:p.A145V). Our qualitative interview study explores these experiences and needs in order to improve counseling and support. Homozygotes develop early onset iron overload. Fredj: None. [SG1]This can be excluded V. Kowalczyk: None. Eight embryos were sampled: Four were carriers for 84GG mutation; 1 aneuploid; 1 had no result; 2 were N370S carriers and thus transferable. Miyatake: None. The interpretation of pathogenicity when considering alternatively spliced isoform will have a direct impact on the affected individuals and their families, it will also help inform on the normal function of MLIP in skeletal muscles. Molday2, Masoud Garshasbi1 1Tarbiat Modares University, Tehran, Iran, Islamic Republic of, 2University of British Columbia, Vancouver, BC, Canada, 3Tehran University of Medical Sciences, Tehran, Iran, Islamic Republic of, 4Royan Institute for Reproductive Biomedicine, Tehran, Iran, Islamic Republic of. N.L. Bowers: None. We also annotated the mQTL-participating CpGs and conducted enrichment analyses with the DisGeNET database. Conclusion: Stringent gene selection for DCM genetic testing reduced the number of VUSs whilst retaining ability to detect similar pathogenic variants. Loron: None. P07.012.D MEFV gene mutation frequency in Georgian FMF patients Dodo Agladze 1,2,3, Lali Margvelashvili2, Saba Iordanishvili4, Maka Ioseliani5, Teimuraz Mikeladze6, Hasmik Hayrapetyan7, Tamara Sarkisian7, Oleg Kvlividze3 1Research Institute of Clinical Medicine, Tbilisi, Georgia, 2Pediatric Surgery Center KidCo, Tbilisi, Georgia, 3School of Medicine, New Vision University, Tbilisi, Georgia, 4Petre Shotadze Tbilisi Medical Academy, Tbilisi, Georgia, 5New Hospitals, Tbilisi, Georgia, 6Caucasus Medical Center, Tbilisi, Georgia, 7Center of Medical Genetics and Primary Health Care, Yerevan, Armenia. This may result in severe dysmorphism, increased intracranial pressure, seizures, visual and hearing defects, psychomotor delay and behavioural anomalies. Maver: None. Rokić: None. Zemková: None. Nectoux: None. Hilger1,3, Phillip Grote8, Benjamin Odermatt2, Heiko Reutter3,9, Gabriel C. Allegri: None. Conclusion: Our results support, that in diploid androgenetic hydatidiform moles, the frequency of aneuploidy is higher in conceptuses showing heterozygosity, than in those showing homozygosity. One patient presented also with a developmental speech disorder, learning difficulties and microcephaly. Next, we ran GWAS on male-specific (N = 18,732) and female-specific (N = 17,322) subsets of the data using linear mixed models. To identify primarily associated variants in MS related regions, we performed a preliminary analysis of co-occurrence of drug target genes in the 201 known MS associated regions querying three drug databases. Senderek: None. In this study, we estimated the proportion of secondary findings of exome sequencing among Russian patients. Methods: UK Biobank European ancestry descent participants (n = 335,909, 40-70 years) were followed up from baseline (2006-2010) via hospitalization records (mean 10.5 years). However, the list of novel phenocopies and potential candidate genes is not final yet. The Richard P. RNA isolated from testicular tissue was used to show that FKBP6 expression levels were severely reduced in both patients, confirmed by immunostaining. Beck-Wödl: None. Exome sequencing (ES) has become a standard test for undiagnosed developmental disorders, now increasingly used in prenatal diagnosis.

Instruments for MR were selected from publicly available GWAS data for sitting-to-standing height ratio, ensuring non-overlap with chronic BP GWAS using UK Biobank. Conclusion: This technique offers a high-throughput method for accurate haplotype and structural variant detection of known and unknown variants of CYP2D6 and CYP2D6-CYP2D7 hybrids. Conclusions: The results highlight the clinical diagnostics potential of a thorough reanalysis of previously negative WES cases. We analyzed telomere length (TL) in metaphases from 67 human embryos, unsuitable for transfer into the uterine cavity due to abnormal ploidy or morphology. To find potential sex-specific or sex-differential associations, we first analyse all cases regardless of sex (all) and then analyse stratified on sex. Conclusions: In NOA cases increased WNT5B mRNA levels suggests an association with increased nuclear β-catenin in postmitotic germ cells and defective spermatogenesis. Background: In less than 5% of cases, Down syndrome (DS,OMIM#190685) is due to translocation.The most common translocations observed are between the long arms of chromosome 21 and another acrocentric. The characterization of the lines showed some common alterations already described in HNSCC, as well as differences that can be due to the location of the primary tumours. Iwanowski: None. After a course of treatment, the patients achieved liquid biopsy and medical imaging examine for an average of 2 to 6 months to monitor cancer recurrence. The mechanism underlying the development of this disease is not well understood yet and the description of more cases will help to a better understanding and clinical characterization. Ongoing in vitro experiments will provide further insights into the mechanistic role of CYR61 in the development of obesity and metabolic dysfunction. We invite PGS submissions and user feedback to ensure the continued development and expansion of the PGS Catalog to meet the community's needs. Introduction: Several ovarian cancer susceptibility genes have been discovered, but more are likely to exist. This substitution is absent in ExAc database and has been classified as variant with uncertain significance. O.E. Talantova: None. Objective: To compare mosaicisms in prenatal chorionic villus samples with corresponding postpartum placental samples. This variant was not reported in population databases (1000G, ExAC, GnomAD) and literature previously. Expression analysis of mRNA MYH3 transcript showed retention of intron 15, which was predicted to lead to an in-frame insertion of 34 amino-acid sequences. Dias2, A. Fernandez4, Monica P. She carried two NTHL1 PVs, c.268C>T p.(Gln90*) and c.235dupG p.(Ala79Glyfs*2). Genu varum was noted at 6 months. Both parents were deceased and no information was available. Strehlow: None. Filatova 1, Natalia S. Moreover, mendelian randomization with eQTL integration has confirmed the involvement of ELOVL7 ($p = 0.046$) with adalimumab response. Immunohistochemistry experiments were also performed in postmortem brain samples from FXTAS patients. van der Post8, Jan Lubinski6, Carla Oliveira2, Nicoline Hoogerbrugge1, Richarda M. Mutation types and frequencies in most of the genes were as expected. Gripp: None. Arroyo-Garrapucho: None. This study aims to genotype 34 neurodegenerative genes that harbour REs, in a cohort of 1000 controls and 1000 patients from the Irish ALS bank to assess the association between expanded genotypes and ALS. Raznahan: None. 13935 of them were included in the analysis. Long non-coding RNA (lncRNA) are acknowledged as important regulators of immune cell differentiation, but the repertoire of non-coding transcripts that control Treg development and function largely remains to be identified. Clinical features in these patients include moderate to severe ID, poor language, movement disorder with ataxia, and sometimes seizures. González-Montelongo: None. Monogenic phenotypes are usually rare and with high penetrance and the phenotypic status is driven by specific mutations. The estimated risk for a hearing loss in the examined individual carrying the microdeletion was estimated as 0.11-0.67% for STRC, 0.016-0.13% for OTOA, and 1.9-7.5% in the DFNB1 locus (including double heterozygocity with GJB2 clinically significant sequence variants). Monhoven: None. Based on statistical features of nonfunctional TCR rearrangements in low biased TCR repertoires we formulated the Over Amplification Rate (OAR) measure as a ratio of observed and expected frequency of a V and a J gene among nonfunctional rearrangements. Speakers Bureau/Honoraria (speakers bureau, symposia, and expert witness); Modest; BioMarin Pharmaceutical Inc, Alexion. Future functional studies will define the underlying molecular mechanisms and further support the impact of these novel findings, thus expanding the current literature on the heterogeneous pathogenicity of NFIB variants. Supported by Ministry of Health of the Czech Republic, grant Nr. NV18-02-00237. The variant is located in 5´UTR and may downregulated expression of BMP4. Analysis included variant retrieval, quality data analysis, genotype to diplotype convertion and pharmacogenetic phenotype classification. The syndrome inherits in a paradoxical manner and exceptionally presents greater severity of symptoms in heterozygous females than hemizygous males. Eich: None. Results: Male p.C282Y homozygotes had lower T2* measures in areas including the putamen, thalamus, and hippocampus, compared to no HFE mutations. HLRCC is due to mutations of the fumarate hydratase (FH, fumarase) gene that encodes for FH enzyme which acts as a tumor suppressor. This study contributes to an improved understanding of the disease processes in SD, and demonstrates the value of quantitative proteomics to differentiate the pathophysiological mechanisms of specific subtypes of dementia. Krawczyński: None. The results indicate potential unequal access to NIPT, which has both ethical and policy implications. opioid users were compared as a reflection of response to NSAIDs, adjusting for relevant co-variates. In addition, some tools do not have a dedicated web interface or can be time consuming for the end-user. M.A. Khan: None. G.P. Lauria: None. No similar phenotype was described in the 22 other patients. Baux: None. Le Duc: None. Dudkina1, Vladislav S. I.B.A.W. te Paske: None. Methods: Small uEVs were isolated by size exclusion chromatography from two urine samples per FD patient ($n = 21$) obtained 5 years apart. A moderate but lifelong genetic Lp(a) reduction translates to a noticeable CAD risk reduction. Balance disorders could involve peripheral vestibular damage. P04.049.B Lipoid proteinosis: A novel mutation in ECM1 gene in a Turkish patient Elifcan Tasdelen 1, Isa An2 1Department of Medical Genetics, Sanliurfa Education and Research Hospital, Sanlıurfa, Turkey, 2Department of Dermatology, Sanliurfa Education and Research Hospital, Sanlıurfa, Turkey. Result: Here we show that multiple genes mapping to this region regulate brain size in contrast to previous studies, with female significantly less affected. Castro1, Pedro G. Sequencing was performed in an Illumina MiSeq System; a customised bioinformatic pipeline was developed for discovery, annotation and filtering of SNVs, indels and CNVs. Sanger sequencing on parental samples was used for segregation analysis of candidate variants. However, 3'-end RNA-sequencing datasets have identified a large number of novel polyadenylation sites, many of which are located outside of annotated exons, suggesting that our current 3'UTR catalogue in human is incomplete. Ownership Interest (stock, stock options, patent or other intellectual property); Significant; Fluent BioSciences. We present the first comparative study of osteoblast differentiation from normal pediatric controls vs OI patients with phenotypic variability. Materials and Methods: The material for the study was blood samples from 36 pregnant women diagnosed with IUGR and 30 healthy women. Hirvonen: A. This phenome-wide mantis-ml resource allows researchers to both identify the top ranked genes associated with a disease of interest (original application) and also to identify the top-ranked human phenotypes for a given gene of interest (extended application). Baschiera: None. It also contributes to the diagnosis of single gene disordersif high resolution array is used. Supported by MEYS 8F20002 EJP RD and the European Union's Horizon 2020 research and innovation programme, EJP RD COFUND-EJP N° 825575. In the current study, we tested four machine learning methods to predict the probability of a positive WES. Funding: IMH RC2019, RC2020 V. Denommé-Pichon*: None. Al-Odaib: None. Materials and Methods: Sequence surrounding the breakpoint was analyzed by Sanger sequencing in 26 out of 27 known Czech families with exon2_6dup and all 8 known Czech probands carrying exon16_18dup. Taking into account that the current knowledge about the phenotype-genotype correlation in this pathology is insufficient, the functional study of this variant is necessary for the correct interpretation of these results and genetic counselling. Mitev: None. Materials and Methods: Direct Sanger sequencing of the LSS gene or Whole Exome Sequencing was performed on individuals affected with hypotrichosis and their family members. Khachaturyan3, Alexandra V. Daftarian: None. Study group included 435 individuals of the Lithuanian origin. In silico analysis of the intronic variant suggested that removed the ATG, thus having a damaging effect at the ORF, based on the 5'UTR location of the variant. Revah-Politi: None. Saletta: None. WGS analysis allowed to redress three genotype. Methods: Retrospective outcome was obtained on 1005 cases with vanished twin/triploidy results, following a SNP-based NIPT's twin validation. P15.008.D Comprehensive carrier screening strategy for challenging genomic conditions Evrim Unsal, Suleyman Aktuna, Leyla Ozer, Merve Polat, Volkan Baltaci Yuksek Ihtisas University, Ankara, Turkey. N.M. Vandevelde: None. Jezernik: None. Macdonald-Dunlop: None. The most common presentation was gait imbalance ($n = 33$) or sensory symptoms ($n = 16$). The role of individual CpG and SNP markers will be tracked in enrichment analysis. All 7 affected individuals investigated carried a maximal 264 kb heterozygous duplication. Mario: None. Despite enhanced knowledge about CFTR genetic confirmation of diagnosing Cystic Fibrosis (CF) sometimes remain difficult due to variants of unknown significance (VUS). Grifantini: None. Chorin: None. Marseglia: None. Falkai: None. The patients need an individualized management, especially for decisions related to sex of rearing, future intervention, hormone treatment and reproductive options. Respondents were evenly distributed across clinical genetics (29.7%), paediatric endocrinology (40.1%) and paediatric cardiology (30.2%). Conclusion: Over a 24-year period, we observed an increasing number of women opting for RRS. Results: We detect 139 pQTLs for 107 proteins, the majority of which (65%) are cis-acting, including 76 independently-associated sequence variants that have not been previously identified. SNP-array was normal. For the numerical abnormalities: 4 cases (0.24%) were with triploidy; 1144 (70.8%) with trisomy 21; 133 (8.23%) with trisomy 18; 86 (5.32%) with trisomy 13; 9 (0.56%) with mosaic autosomal trisomy; 66 (4.1%) with 45,X; 91 (5.6%) with 47,XXY; 12 (0.74%) with 47,XXX; 6 (0.37%) with 47,XYY; and 65 (4.0%) with a mosaic sex chromosome aberration. Thirty percent of our unsolved cases receive a result based on literature, animal studies and other information. Many centres have rapidly replaced face to face consultations with video and telephone consultations. López-González: None. Genetic testing identified a heterozygous pathogenic variant in the MECP2 gene, NM_001110792.1: c.1195_1246del; p.(Pro399Serfs*5). P08.067.A New cases from Spanish population with intragenic pathogenic variants in SETD5 gene: refining the phenotype and expanding the genotype María José Sánchez Soler 1, Fernando Santos-Simarro2,3, Sixto García-Miñaúr2,3, Ana Teresa Serrano Antón1, Verónica Seidel4, Graciela Pi Castán5, Marta Pacio-Míguez2, María Palomares-Bralo2,3,6 1Medical Genetic Section, H. The obtained SNP and methylation data will be used in statistical analyses. Here we report on the outcome of one year hereditary cancer predisposition testing using the Hereditary Cancer Solution developed by Sofia Genetics, an NGS-based capture panel optimized for the detection of SNVs, InDels, and CNVs in 26 genes. Schmidt: None. Employment (full or part-time); Modest; Bumrungrad Hospital. Materials and Methods: Whole exome sequencing was performed on two DNA pools, one composed with DNA from 90 unspecified dementia patients and the other - a control pool with DNA from 100 age-synchronized healthy individuals. Somatic insertions were detected in cancer types, such as colorectal, lung, or breast carcinomas. Previous work from our group implicated this gene in ENS development by showing enteric aganglionosis in mab21l2-/- mutant zebrafish embryos. R.L. Nussbaum: A. Pesevska1, A. P03.019.C Familial case of Cystic Fibrosis with genotype-phenotype correlationsTinatin Tkemaladze1,2,3, Mariam Ghughunishvili 4,5, Eka Kvaratskhelia1,5, Elene Abzianidze1, Volha Skrahina3, Arndt Rolfs3,6,7 1Department of Molecular and Medical Genetics, Tbilisi State Medical University, Tbilisi, Georgia, 2G. Gentle University of the Witwatersrand, Johannesburg, South Africa. RNA-seq data was analyzed implementing previously established pipelines. Biological sample (blood) was collected and Next Generation Sequencing was performed, using Illumina TruSight One sequencing panel, which includes 4813 genes. Adherence to diet was irregular, she drank beer intermittently, and during the last year she also used oral contraceptives for six months. Regional Health Management of Castilla-and-Leon: GRS1547/A/17 and GRS175/A/18 M. Non-invasive prenatal diagnosis was performed using custom assays for droplet digital PCR. Zudina: None. Background: The genetic cause of dilated cardiomyopathy (DCM) remains unexplained in a substantial proportion of cases. This new version emphasizes on the manipulation of NGS data for interpretation and use of bioinformatics algorithms. P10.031.C Partial uniparental disomy of chromosome 4 causes by homozygous TRAPPC11 truncating variant Nawale HADOUIRI 1,2, Véronique Darmency3, Véronique Dulieu2, Marie-Gabrielle Mourot De Rougemont4, Benoit Collomb5, Stéphanie Perez Martin6, Olivier Blanchard7, Antonio Vitobello8, Christophe Philippe9, Laurence Faivre1,10, Christel Thauvin-Robinet1,11,12 1UMR1231 GAD, Inserm - Université Bourgogne-Franche Comté, Dijon, France, 2Pôle rééducation-réadaptation, CHU de Dijon, 23, rue Gaffarel, Dijon, France, 33- Service de Neurophysiologie Clinique, Hôpital d'Enfants, CHU Dijon Bourgogne, Dijon, France, 44- Hôpital Francois Mitterrand, département de radiologie diagnostique et thérapeutique, CHU, 14, rue Paul Gaffarel, Dijon, France, 55- Unité de Réanimation polyvalente, Hôpital d'Enfants, CHU Dijon Bourgogne, Dijon, France, 6Pôle pédiatrie, Hôpital d'Enfants, CHU Dijon Bourgogne, Dijon, France, 7Service de Pédiatrie, Centre Hospitalier de Roanne, Roanne, France, 8Unité Fonctionnelle Innovation en Diagnostic génomique des maladies rares, FHU-TRANSLAD, Dijon, France, 98- Unité Fonctionnelle Innovation en Diagnostic génomique des maladies rares, FHU-TRANSLAD, Dijon, France, 109- Centre de Référence maladies rares « Anomalies du Développement et syndromes malformatifs », centre de génétique, FHU-TRANSLAD, CHU Dijon Bourgogne, Dijon, France, 1110- Centre de Référence maladies rares « Déficiences Intellectuelles de causes rares », CHU Dijon Bourgogne, Dijon, France, 12Unité Fonctionnelle Innovation en Diagnostic génomique des maladies rares, FHU-TRANSLAD, CHU Dijon Bourgogne, Dijon, France. The dataset with solved and unsolved cases had been enriched with data about clinical phenotype, severity and co-morbidities as well as time course and family history. HNRNPR code the heterogeneous nuclear ribonucleoprotein R, involved in RNA expression of human development homeobox and T-box genes. Another affected gene found in our patients was BRCA1. MLPA and array-CGH analysis showed a normal dosage of these exons and an increased dosage of flanking exons 1-15 and 30-34. However, there were several variants in other genes that require further investigation. Hoogerbrugge*: None. Conclusion: Based on the available published literature about genetically proven Noonan Syndrome, it appears likely that the lifetime prevalence of lymphatic disorders in Noonan syndrome is more than the generally accepted 20%. The development of the cerebral cortex is a complex and dynamic process. Aliyev: None. P11.124.B Unravelling terminal 6p deletions with the help of social media Eleana Rraku 1, Aafke Engwerda1, Jennifer Geurink1, Laura Monsma1, Pauline Bouman2, Morris A. Cremers1, Peter A. Despite the extensive research, bioinformatics prediction of microRNA binding sites remains a challenge. S.B. Arslan Satılmış: None. The variant at LDLR, c.*653G>C showed a 40% less luciferase activity than WT. Chromosome disorders form a major category of genetic disease. Association of peripheral neuropathy has rarely been described and a pathogenic SAMD9L variant causing Charcot-Marie-Tooth (CMT) disease has been reported only once. We suppose that a measure of cfDNA fragmentation in differentially fragmented regions could serve as a cancer biomarker. This results in penetrance estimations for neurosusceptibility loci that are approximately 5-fold lower in some instances. Introduction: Congenital heart disease (CHD) is the most common birth defect, affecting nearly 1 per 100 newborns. Slavova-Marinova: None. This example confirms the advantage of a wider WES-based strategy over custom panels and illustrates the importance of a careful phenotyping before the analysis. Pérez-Dueñas: None. The diagnostic yield of at least one actionable variant (pathogenic/likely pathogenic) was 28%, while at least one variant of uncertain significance (VUS) was detected in 27% of the cohort. Almutairi: None. Revising CMA, long runs of homozygosity (ROH), including these two genes, were found. L.A. Vázquez-Pérez: None. Christopoulou: None. P17.086.A Phenotype based prediction of WES outcome using machine learning Alexander J. We used NGS custom panel approach to scan the lesions-associated genomic events using blood, buccal brush, fibroblast and rhabdomyosarcoma tissue samples. No parental consanguinity was reported. The missense variant was absent from ethnicity matched healthy controls and available public databases. All are splicing or frameshift variants with premature stop codons and predicted to result in a premature termination within Dhc-C domain of DVL3. Asensio: None. Her daughter had mild symptoms of hEDS. Whole-exome sequencing (WES) enables the simultaneous analysis of all coding regions of the human genome. Our sequencing data showed that the automated libraries covered >93% targeted regions and >97% of the reads aligned with the reference. Moreover, the general population participants answered to a genetic knowledge questionnaire. Peripheral blood mononuclear blood cells of 10 patients with severe late complications from radiotherapy and 10 patients without symptoms were mock-irradiated or irradiated with 8-Gy. The 48-h response was analysed by gene expression profiling with Affymetrix Human Exon 1.0 ST arrays. M.P. Hommersom: None. Berrocal-Navarro: None. The aim of our study was to investigate correlations of expression of ncRNAs and genes of epigenetic regulation in gastric cancer. Rare copy number variants (rCNVs) are the common genetic cause of Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) and could harbour miRNAs. The aim of this study was to investigate to which extent rCNVs associated with CAKUT harbour miR-548 members. Rath: None. All index patients with predicted loss-of-function mutations were female and had PLE on lower extremities. Golubenko1, Maria S. P04.063.D Search for exonic homozygous/compound heterozygous variants in affected sib-pairs identifies novel candidate genes for nonsyndromic cleft palate Nina Ishorst 1, Helena Shkuro1, Julia Fazaal1, Ann Kathrin Hoebel1, Holger Thiele2, Teresa Kruse3, Michael J. Conclusion: Actionable variants were more likely to be detected in females in our cohort. Dubis: A. J.T. den Dunnen: None. Eysteinsson: None. Bodnev, Anastasia A. CHEK2 protein regulates the cell cycle and is activated in response to DNA damage. There were no oculocutaneous telangiectasia and immunodeficiency reported. We discovered and replicated 31 associated loci, 16 of which are novel. Vidaud: None. Together, this work expands the phenotypic and molecular spectrum associated with SETD1B variants, provides insights into their functional effects and will ultimately facilitate the counseling regarding the clinical spectrum of newly diagnosed patients with the SETD1B-related syndrome. U.F.H. Engelke: None. P03.009.A Association of KEAP1 polymorphism with autoimmune thyroiditisCristina Robles Lázaro1,2, María Ovejero-Sánchez 3,2,4, Nerea Gestoso-Uzal2,3,4, Carlos Gutiérrez-Cerrajero2,3,4, Paloma Martín-Bejarano Soto2,3,4, Pamela Vázquez-Cárdenas3,2,4, Ana Belén Herrero2,3,4, Rogelio González-Sarmiento2,3,4 1Endocrinology Service, University Hospital of Salamanca, Salamanca, Spain, 2Molecular Medicine Unit, Department of Medicine, University of Salamanca, Salamanca, Spain, 3Institute of Biomedical Research (IBSAL), Salamanca, Spain, 4Institute of Molecular and Cellular Biology of Cancer (IBMCC), University of Salamanca-CSIC, Salamanca, Spain. The c.155del change was the most frequently found variant (65% of cases). We describe a 5-year-old girl and her mother with a previously unreported frameshift variant in TAB2 identified by whole exome sequencing (WES). Introduction: Parkinson's Disease (PD) is a neurodegenerative disorder associated with genetic alterations in cc. P19.057.A The Trisomy 21 Prevalence in the Moscow Region of Russia Nataliya Demikova 1,2, Elizaveta E. Sullivan4, Vandana Shashi4, Maha S. Keene: None. M.A. Restrepo-Córdoba: None. P12.039.C Functional analysis of rare CHEK2 variants identified in breast cancer patients Olivia Fuentes Rios 1,2,3, Marta Santamariña2,3,4, Ángel Vizoso5,6, Belinda Rodríguez1,3,4, Ana Crujeiras1,3, Ana Paula Vega Gliemmo1,3,4 1Instituto de Investigación Sanitaria de Santiago de Compostela, Santiago de Compostela, Spain, 2Universidad de Santiago de Compostela, Santiago de Compostela, Spain, 3Fundación Pública Galega de Medicina Xenómica, Santiago de Compostela, Spain, 4Centro de Investigación en Red de Enfermedades Raras, Madrid, Spain, 5Universidad de A Coruña, A Coruña, Spain, 6Centro de Investigaciones Científicas Avanzadas, A Coruña, Spain. There is a large prevalence of microcephaly, higher in PTPN11, associated with ID and behavioral alteration, not previously reported. Ustinova: None. Mayeur: None. Introduction: Mycosis fungoides (MF) is the most common subtype of cutaneous T-cell lymphomas. Patient 2 showed mosaic interstitial deletion of the 22q13.31q33 region, excluding SHANK3 gene. Novo: None. Conclusions: This study revealed an association among the SNPs COL1A1 rs1107946 (TT genotype) and rs1800012 (TT genotype) and MSST injuries in Lithuanian athletes. Conclusions: We provide detailed clinical information on a patient with a biallelic truncating variant in CCDC186 and illustrate the phenotypic similarities to the previously reported patient. Proshlyakova: None. P05.008.B A FAIR Brugada Syndrome data repository to facilitate cardiogenetic research Marta M. Our patients with WDR26-related syndrome had a pronounced subpalpebral crease, rounded palpebral fissures and relatively large irises, not described previously. Segregation analysis is ongoing. Conclusions: The high DNA 5mC and low H3K4me3 levels are markers for properly-protaminated spermatozoa, documenting the correct spermatogenesis. Grants: FIS-PI20/01053 J. (2020) Science Advances, DOI: 10.1126/sciadv.aba1862. Another placental key factor of IUGR physiopathology is angiogenesis. P02.014.C Congenital insensitivity to pain: molecular characterization of a novel disrupting mutation in SCN9A Margherita M. Here we combine different approaches and extend the detection method based on MIEs using approaches from Baysian machine learning. Nyboe: None. (2019) as base file and European individuals from 1000 Genomes ($N = 503$) as reference for clumping. Single-nucleotide polymorphisms in the xenobiotic biotransformation genes CYP1A1 (rs1048943), CYP1A2 (rs762551), GSTP1 (rs6591256, rs1871042 and rs17593068) were detected by the real-time polymerase chain reaction. Our results indicate that WFS1 and MYO7A have the highest prevalence in the Spanish population (6.48%) followed by MYO6A (5.56%).We conclude that OTO-NGS-v2 is a robust diagnostic tool for the genetic diagnosis of hereditary hearing loss. Baig: None. P09.027.D Mitochondrial DNA influences the susceptibility to Autism Spectrum Disorders and the severity of the clinical phenotypeLeonardo Caporali1, Claudio Fiorini1,2, Flavia Palombo1, Flavia Baccari3, Martina Romagnoli1, Paola Visconti4, Annio Posar4, Maria Cristina Scaduto4, Elena Maestrini5, Cinzia Cameli5, Marta Viggiano5, Anna Olivieri6, Antonio Torroni6, Elena Bacchelli5, Magali Rochat7, Valerio Carelli1,2, Alessandra Maresca 1 1IRCCS Istituto delle Scienze Neurologiche di Bologna, Programma di Neurogenetica, Bologna, Italy, 2Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy, 3IRCCS Istituto delle Scienze Neurologiche di Bologna, UOSI Epidemiologia e Statistica, Bologna, Italy, Bologna, Italy, 4IRCCS Istituto delle Scienze Neurologiche di Bologna, UOSI Disturbi dello Spettro Autistico, Bologna, Italy, Bologna, Italy, 5Department of Pharmacy and Biotechnology, University of Bologna, Italy, Bologna, Italy, 6Department of Biology and Biotechnology "L. AlHindi: None. Conclusion: Expression of CMT-causing mutations caused similar signs of toxicity in four CMT-related aaRS, rendering our models a valid platform for investigating putative shared molecular pathway(s). Janonytė: None. O.M. Vanakker: None. Patient-derived hiPSCs can be a long-term source for a variety of different cells and significantly contribute to the development of complex skin disease models, ultimately facilitating the translation of therapeutic approaches into clinical studies. TR variation characterization in the Slovenian population yielded informative results for 73,893 alleles in 17 TR regions and was limited to coding, UTR, and several well-covered non-coding regions. Greenwood: None. Yet, when a patient does not consent to the disclosure of genetic information to relatives, it is unclear how healthcare professionals (HCPs) should balance their responsibilities towards patients and their family members and whether breaches in confidentiality are warranted. Her karyotype is 46, XY. Additional studies are required to evaluate its role in male infertility. We believe that the translocation breakpoints disrupt an essential gene, and the gene is inactivated and behaves as a point mutation, which could explain the phenotype. Sloots1, René M. Conclusion: In addition to a novel association, we replicated associations previously reported both at pathway and gene specific level, suggesting a robust genetic component of HGS at different ages. Darbar: None. (Nguyen et al, Am J Hum Genet, 2020). Telomeres were detected by qFISH (Telomere PNA FISH Kit/Cy3, Agilent). With a genetic diagnosis patients can take action on inheritance patterns and disease progression. Results: The following main topics were highlighted: uncertainty; government support and regulation; the professional community problems; ethical limitations and responsibility to patients; expectations, fears and prejudices of people. A predominance of PMM2-CDG was detected as in other countries. Whole genome sequencing revealed a homozygous 22.6Kb deletion encompassing the promoter and first exon of ERGIC1. Vives-Usano: None. We have developed a strategy to detect and prevent the issues derived from such stressors. They would have gone overlooked if we only have screened BRCAs genes. Most cases (86%, 799/934) were analysed using the Comprehensive Hearing Loss and Deafness Panel (239 genes), while a minority (14%, 135/934) were analysed using smaller panels. Cell-free DNA (cfDNA) is found in many bodily fluids and is believed to derive primarily from apoptosis of hematopoietic cells. Our work presents a framework for systematic exploration of mediators in MR. Prokisch: None. Identification of heterozygous TERT mutation and short TL in extended family members, segregating with the phenotype, highlighted disease anticipation and further confirmed the diagnosis of DC. The results confirm that TRs represent an important source of human genetic variability which can be partly detected using ES, however, larger whole-genome sequencing studies are required for their genome-wide characterization. In particular, heterozygous nonsynonymous substitution in the INSR gene (GRCh37/hg19, chr19 (19p13.2):7174702, c.DNA: c.1015T>C, protein: p.Cys339Arg) was identified, and it was confirmed by Sanger sequencing. PLS3 mutations cause X-linked osteoporosis with fractures. Rubio-Rodríguez5, Beatriz Guillen-Guio1, Jose M. Genu varum is milder and knee pain is more common as compared to other metaphyseal dysplasias. We identified a proxy SNP in GWAS data, confirmed linkage disequilibrium (LD) experimentally (PFGE) and determined p.Arg21Ter frequencies in the 1000 Genomes project (1000G). However, further studies are needed in order to better characterize the phenotype and establish genotype-phenotype correlation. Frebourg: None. Here, we present phenotypes of adCRD, adCRD and arCSNB in three Bulgarian families carrying different pathogenic variants of GUCY2D. Inositol polyphosphates are vital metabolic and secondary messengers, involved in diverse cellular functions. Results: Five 3'UTR LDLR variants were selected for characterization. He had an elder sister with laryngomalacia requiring tracheostomy in childhood, and late-onset epilepsy; and a younger brother with cerebral palsy after cardiac arrest at 3 months, hypotonia, and hyperlactacidemia. Krapivin, Anna A. Lederer: None. Veldink2, Russell L. Results: We provide penetrance estimation curves associated with SORL1 LoF variants at the digenic level. Introduction: Coronary artery disease (CAD) is the leading cause of death worldwide. van Reekum: None. Employment (full or part-time); Significant; Miroculus, Inc.. Severe neurodevelopmental phenotypes were present in two individuals, and variably penetrant in family 1, supporting that this can be an important feature of the ALDH1A3 syndrome. A.A. Kubanov: None. Boban: None. P11.102.D A 3,195 kb duplication at 2q14.3 in a proband with a t(17;19)(p13.1;p13.3)mat is most likely associated with craniofacial dimorphisms, developmental and neurological anomalies Natália Oliva-Teles 1,2,3, Mariana Marques4, Manuela Mota-Freitas1,2, Cristina Candeias1,2, Joana Fino4, Ana Fortuna1,2, Dezso David4 1Centro de Genética Médica Doutor Jacinto Magalhães/Centro Hospitalar Universitário do Porto, Porto, Portugal, 2Unit for Multidisciplinary Research in Biomedicine, Institute of Biomedical Sciences Abel Salazar, University of Porto (UMIB/ICBAS/UP), Porto, Portugal, 3Departamento de Medicina da Comunidade Informação e Decisão em Saúde, Faculty of Medicine, University of Porto, Porto, Portugal, 4National Health Institute "Doutor Ricardo Jorge", Lisbon, Portugal. Chaturvedi: None. Preliminary results: We obtained 61,105 significant placental mQTLs from which, 39,284 of these were located inside one or more genes. Five patients suffered from recurrent onychocryptosis that required surgical procedures, as an unreported medical condition. Introduction: Abnormalities of the immune system are rarely reported in patients with RASopathies. Roque: None. None of the tested variants located in the transactivation domain were found to have effect on the HNF1α activity. MAN2B1 gene was analysed by Sanger sequencing. Introduction: The role periodontal pathogens in atherosclerosis has not been fully understood. Conclusions: So far only one case of homozygous missense mutation has been described causing the Lennox-Gastaut syndrome. The mitogen-activated protein kinase (MAPK) signaling pathways are involved in key physiological processes such as cell proliferation, differentiation, apoptosis, survival, gene expression, and cell motility. Burnytė: None. This report brings to our attention that 2q32q33.3 microdeletion can be associated with immune alterations. We found that A>C and T>G transversions are enriched in NovaSeq data. García-Serra: None. Carreira3,4,5 1University of Coimbra, Faculty of Medicine, Coimbra, Portugal, 2Cytogenetics Laboratory, Medical Genetics Unit, Pediatric Hospital, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal, 3iCBR- CIMAGO/CACC – Center of Investigation on Environment Genetics and Oncobiology of iCBR/ Clinical Academic Center of Coimbra, Faculty of Medicine, University of Coimbra, Coimbra, Portugal, 4Cytogenetics and Genomics Laboratory, Faculty of Medicine, University of Coimbra, Coimbra, Portugal, 5CIBB- Center for Innovative Biomedicine and Biotechnology, University of Coimbra, Coimbra, Portugal, 6Medical Genetics Unit, Pediatric Hospital, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal. The J2 haplogroup is supported by the conventional analysis of a known recent descendant on the direct male line of H.I.H. Prince (Şehzade) Yusuf Izzeddin (1857-1916), the first-born son of Sultan Abdülaziz (1830-1876) and the older brother of Abdulmejid II (1868-1944). Associated CAKUT, ocular, skeletal and dental anomalies were variably observed. Material and Methods: Relative telomere length was measured in DNA isolated from the blood samples using a real-time polymerase chain reaction approach. M.D. Oliver: None. Sarosiek: None. P24.030.A Genome-wide age at onset analysis discovers association of the ApoE locus with earlier onset of ischemic stroke Joanna von Berg 1, Braxton Mitchell2, Steven Kittner2, Jeroen de Ridder1,3, Sander W. In 31.0% of patients, carrier screening tests were recommended or added. Exome-wide genetic analyses, considering all protein coding genes, could increase diagnostic yield, but at the cost of turn-around times. Four samples with known expanded STRs were also flagged with Expansion Hunter. Since a normal intracellular folding and secretion rate of type I procollagen was observed, this overmodification cannot be explained by prolonged exposure of the procollagen molecules to modifying enzymes, as is commonly observed in other OI types. Introduction: The implementation of next-generation sequencing in the clinical setting has increased the diagnostic yield of Hereditary Breast and Ovarian Cancer Syndrome (HBOC). In our first analysis we focused on the protein-coding regions and are currently applying technical, pedigree-based and frequency filtering in each of the families. Benoit: None. This confirmed skipping of exon 4 affecting the FHA- and phosphatase-domains of PNKP (p.Leu67_Lys166del). V.S. Dudkina: None. Banjac: None. Ghayoor Karimiani: None. Girisha30, Thomas Haaf4, Jenny C. Goldberg: None. Badenas: None. Siemann: None. As our previously described patient, these two patients presented complex ASD phenotype. Materials and Methods: According to the sample availability, we performed testing of the tumor-FFPE and blood/non-tumor-FFPE samples in one LS suspected family. Caraffi 1, Gabriele Trimarchi1, Sara Giangiobbe1,2, Chiara Cattani1, Benedetta Cavirani1,3, Michela Malacarne4, Francesca C. Intelligence was normal. Popa" University of Medicine and Pharmacy - Department of Medical Genetics, Iasi, Romania. Leenders2, Barbara Frentz3, Paulien A. We aimed to assess the spectrum of germline pathogenic variants in cancer susceptibility genes among Spanish patients selected for personal and/or family history of breast, ovarian, prostate, melanoma, and other BRCA-associated cancers. Grishchenko, Tatiana V. However, significant changes in the expression at the mRNA level for the DNM2 gene were obtained in the group of treated patients with PD. Fratzl: None. Boni: None. of Pediatric Endocrinology, Hospital Sant Joan de Déu, Barcelona, Spain. Conclusions: Together these five cases show that constitutional heterozygous POLE driver-mutations cause a phenotype distinct from PPAP but resembling CMMRD due to the associated childhood/adolescent malignancies and non-malignant features. For instance, the prediction R2 (adjusted for sex, age, and 20 genetic PCs) for the three most prevalent psychiatric disorders in the IPSYCH cohort ADHD, autism, and depression was 1.1%, 0.4%, and 2.6% when using the single-outcome PRS (excluding IPSYCH samples), and 9.1%, 4.0%, and 4.3% respectively using multiPRS. We evaluated the yield of publicly funded clinical WES, performed in a single tertiary referral center during a three-year period (2018-2020). Grant details - UK Medical Research Council award MR/S009892/1 (Principal investigator David Melzer). One female was an FMR1 pre-mutation carrier (1/63). These insights are complemented by an increasing recognition of the functional importance of transcriptional activity outside of known exons, particularly in human brain tissues. Tritto: None. Génin: None. Introduction: High-throughput sequencing of T-cell receptor (TCR) repertoires is widely used to investigate adaptive immunity genomics. Voorhoeve: None. Introduction: Copy number variants (CNVs) play an important role in many biological processes, including the development of genetic diseases, making them attractive targets for genetic analyses. In particular, oncogenic hotspot FGFR1 mutations p.N546K and p.K656E have been demonstrated to play a critical role in the etiology of low-grade gliomas (WHO Grade I/II). F.S. Alkuraya: None. den Dunnen6, Deborah Ritter7,8, Sharon Plon7,8, Marc Greenblatt9, Ian Frayling10, Finlay A. Furthermore, OGM detected repeat expansions in Fragile X and repeat contractions in FSHD. The father underwent GH therapy in childhood, with poor results. At last follow-up (4 years of age), he presented a persistent muscular weakness, severe microcephaly, seizures, delayed developmental milestones and thin corpus callosum. About 10% of all colorectal cancer (CRC) tumors are diagnosed in this cohort of patients (under 45 years). Osipova: None. Thereby, our cellular models may present reduced TTBK2 kinase activity. It can help to avoid financial costs and stress for probands and families. of Molecular Oncology, Riyadh, Saudi Arabia, 16Gaziosmanpasa University, Dept. Gotthardt: None. Results: Three families with pathogenic variants were reported in this work. 1500). González-Neira: None. We further confirmed the apparent transcript escape of the nonsense-mediated mRNA decay pathway. With a finite workforce laboratories may face a lack of resources for analysis of complex cases, leading to an extended diagnostic odyssey for patients and their families. Eight loci are associated with this clinically and genetically heterogeneous disorder. MedExome analysis using NextSeq (Illumina). S.B. Wortmann: None. T.F.M. Andlauer: None. P11.077.C Biallelic truncating variants in MAPKAPK5 cause a new developmental disorder involving neurological, cardiac, and facial anomalies combined with synpolydactyly Denise Horn 1, Elisa Fernández-Núñez2, Ricardo Gomez-Carmona2, Ana Rivera-Barahona2,3, Julian Nevado3,4,5, Sarina Schwartzmann1, Nadja Ehmke1, Pablo Lapunzina3,4,5, Ghada A. N.R. Valiakhmetov: None. Roth: None. R.C. Betz: None. We applied Chi-squared test. Dias1, Leticia Benevenutti1, Felipe R. Ginete: None. Conclusion: Our results will help to better identify families with genetic predisposition to PRCC1 tumors and support the fact that the clinical presentation is a strong argument to be considered to classify novel MET gene missense variants especially when functional assays aren't accessible. Accordingly, we studied the associations between 8 polymorphisms from AGTR1, ACE2 and ACE genes and the severity of the disease produced by the SARS-Cov-2 virus. Introduction: Stickler syndrome (STL) is a clinically and molecularly heterogeneous connective tissue disorder that includes ocular impairment, hearing loss, joint and craniofacial abnormalities. In particular, the effect of the OR-KO burden was higher in younger individuals (aged≤57). Kawashima: None. Al-Shidi: None. Few patients in Russia are over 55 years of age. Trafeli: None. All three siblings had bilateral basal ganglia calcifications.Family 2: A female neonate, with a prenatal diagnosis of HCM, died at 40 days from hyperlactacidemia and severe HCM. This data enriches the spectrum of clinical manifestations in 3pdel/3qdel chromosomopathy. Previous studies have found significant links between insomnia and pain symptoms including both general pain and specific diseases such as migraine. We used nanoparticle tracking analysis to determine uEVs size and concentration. That influences on the load and spectrum of hereditary pathology and the nature of genetic and demographic processes in populations. Romera-Lopez: None. A comprehensive literature search for PPP1R35 mutations yielded two probands affected with severe microcephaly (-15 SD and -12 SD) with the same homozygous indel from a single, consanguineous, Iranian family from a cohort of 404 predominantly Iranian families. Schoumans: None. Jaillard: None. We identified 4 different ATM variants in our patients: 3 previously reported mutations, and one novel variant. D.G. Monckton: None. Molday: B. Sleptcov: None. In this work, we aimed to investigate the differentially expressed genes (DEGs) in T cells in MS using bioinformatic tools and to identify the miRNAs regulating these genes. Nevertheless, given the high rate of false positives, this strategy requires confirmation by another methodology of all clinically relevant CNVs detected. OGM results were compared with available CBA, FISH and CMA (ThermoFisher) data. Ferraz: None. This clinical entity is classically described as an arrhythmic condition occurring in a structurally normal heart, but this assumption has been recently contradicted by several observations, which suggest a link between BrS and structural cardiomyopathies. McLean27, Stylianos E. Steffann: None. Galjaard: None. Introduction: The increase in resolution and coverage of aCGH is of particular importance for genes implicated in neurodevelopmental disorders that are subject to copy number variation (CNV). Chung: None. Imputation and quality controls were applied in 1,333 patients and with more than 7 million common genomic variants. Relative risks of the outer quartiles compared to the middle 50% were determined. Conclusion: Our results confirm that PJS is often associated with truncating mutations in the kinase domain of the STK11 gene, which should be identified for an adequate genetic counseling. Research findings of the association between circadian rhythm gene polymorphisms and MetS and its comorbidities are not consistent. Arasimavicius: None. Ghukasyan: None. No other effects were present after adjustment for these amino acids. Patients are eligible if a monogenic cause for their illness is suspected, a trio structure is available, and a timely genetic diagnosis might alter clinical management. All somatic mutant BRCA1/2 tumours were classified as high-grade serous carcinomas. Conclusions: Overall, our analysis highlights central molecular pathways for pregnancy-related traits and suggests a need to use more accurate and sophisticated association analysis strategies to robustly identify genetic risk factors for pregnancy complications. P12.132.D Comprehensive analysis of correlations in expression of miRNA genes and immune checkpoint genes in bladder cancer cells Przemyslaw A. Beitsch3, Edward D. Aim: To set clinical and genetic correlations of retinal pathology by ABCA4 gene mutations, considering the functional state Material and methods: 15 Russian patients aged from 7 to 32 y.o. with inherited eye diseases ABCA4-associated. Here we describe six patients with a de novo variant in the GAR domain of MACF1, of which five have not been reported before. Those miRNA genes and their targets were included in over-representation analyses in ConsensusPathDB-human. The network predicted age with a RSME of 4.45 years in the test set and identified the genes NRCAM, C19orf57 and MEG1 as most predictive. Individuals who went on to develop adenomatous polyps or CRC were identified by record linkage. Brain MRI revealed cerebellar atrophy, laboratory testing increased alfa fetoprotein - 157 kU/l (normal value 0-7,89). The blood-derived DNA sample was analyzed using Affymetrix® CytoScanTM 750K Array (Applied Biosystems) that includes 550 k non-polymorphic and 200 k SNP markers. Furthermore, the mtDNA haplogroup background might be also relevant for the rate of mtDNA variants emergence in iPSCs. The patients age clearly impacted on the load of somatic variants in parental fibroblasts, but tended to vanish with number of passages in iPSCs. Importantly, we show that also the differentiating step to NPCs may be affected by similar issues. No other samples revealed novel candidate HRD-associated genes, selected on their co-evolution with HR genes. Methods: We typed a novel putative splicing mutation ("KIV-2 4733G>A") in the German Chronic Kidney Disease study ($n = 4{,}673$) by allele-specific real-time PCR and created minigenes. The study aims to analyze the frequency of MEFV mutations in individuals suspected for FMF and determination of SAA1 polymorphism in diagnosed patients, in order to estimate FMF prevalence in Georgia. In this pilot we compared the performance of array-based genotyping with previously clinically determined pathogenic mutations, for 240 breast cancer cases. Singh: None. A.M. Lucassen: None. XP-EHH and iHS tests were performed after genotyping of 36 Tibetans (18 from each altitude) to detect natural selection. Additional disease-driven mechanisms were explored through a review of the literature and several tools, including Reactome, String and GeneCards. Halstead: None. However, with the advances in clinical molecular genetic diagnostic techniques, more patients, especially patients with milder phenotypes, are being diagnosed from detecting pathogenic mutation. We identified the homozygous frameshift variant c.207_208dupTG; p.(Ala70Valfs*7) in the two affected members of family 1 and the homozygous 1-bp duplication c.1077dup, p.(Leu360Serfs*21) in the patient of family 2. P11.071.A Expanding the KIF4A-associated phenotype Silvia Kalantari 1,2, Norah Alsaleh3, Ghada M. Conclusions: Assessment of genome-wide androgenetic mosaicism requires multiple laboratory approaches and an extension of the current diagnostic process and caution to low rate of mosaicism. Artifacts were removed by primers redesign after each iteration of library sequencing and analysis. Kadnikova: None. M.I. Nasir: None. Results: This study investigates PGT-M results of 10 couples carrying different rare genetic conditions and 10 causative genes presented in Table 1. Jones: None. Materials and Methods: Sixteen affected relatives of a large Gypsy pedigree segregating adRD were examined clinically by standard ophthalmological methods. Shamanskiy: None. Chatzovoulou: None. P04.007.D Shared Runs of Heterozygosity Mapping using whole genome sequencing reveals a complex structural variant in GSN causing novel cutaneous-visceral organ Gelsolin amyloidosis Adam Jackson 1,2, Glenda Sobey3, Ashutosh Wechalekar4, Dorota Rowczenio4, . Conclusions: Data generators might use data sharing platforms primarily for collaborative modes of working and network building, such as to find similar cohorts. Studies in mouse Ywhae-/- revealed craniofacial characteristics and numerous brain structural defects (thin cortices, corpus callosum dysgenesis and hydrocephalus) paralleling those seen in the human condition. Future developments of HDL with different extensions can also be explored via HD Hub. Al-Yahyae: None. CLN2 disease often presents with epilepsy between 2 and 4 years of age, accompanied by history of language delay; however, diagnostic delays are common. It generates >40 isoforms. To determine whether the formers are true HRD positives we are currently testing these samples for other (epi-)genetic aberrations explaining their potential HRD-positivity. The glycine conjugation pathway is involved in the metabolism of natural substrates as well as the detoxification of xenobiotics. Finkel17,18, Amanda Gerard11,19, Julie S. The results were compared using a European BCG adult cohort ($n = 300$). Vuruskan: None. Bonnet: None. Krasnov: None. Solve-RD received funding from EU Horizon 2020 (No.779257). Material and methods: Culture of human peripheral blood leukocytes was used. Validation of prioritized variants was performed using Sanger sequencing. Carmody: None. While unusual facial gestalt and some degree of developmental delay is observed in both conditions intestinal lymphangiectasia and lymphedema have been considered exclusive for HS. In non-invasive samples, hs-MSI scores were positive in 2/2 cervical samples and in 1/2 cervico-vaginal self-samples from LS women with EC. RNA-Seq is currently being validated by RT-qPCR and western blot and the functional significance of pathways investigated. Unfortunately, there is no definitive treatment. The second patient, 13 y.o. girl with psychomotor delay, hepatopathy, episodes of lactic acidosis, ketonuria, had novel homozygous intronic variant c.1983-116C>T revealed on WES. A better knowledge of AS clinical features will allow an earlier diagnosis and an adapted care.The determination of the genetic mechanism refines the genetic counselling. Kyriacou: None. Results: Parents were generally positive about WES. Trivisano: None. Sundqvist: None. We assumed that there are genetic markers for neuropsychological disorders development in PD patients among polymorphic variants of genes of the dopaminergic and serotoninergic systems. Friend: None. Fockema Wurfbain 1, M F. De Brasi: None. Methylation patterns included changes in methylation in 72 genes. European Reference Network ITHACA is developing a "meta-registry" called ILIAD, connecting 37 HCPs, databases, and biobanks in 13 countries for patients with dysmorphic/MCA syndromes and/or intellectual disability. Conclusions: OTOG is a frequent gene in FMD and some families with shared variants showed an autosomal recessive inheritance consisting of compound heterozygous missense variants. All epimarks levels were highest in properly-protaminated spermatozoa (both groups). The families were analyzed using an "augmented" panel including the major colon cancer genes with their intronic and flanking genomic regions. Other common features are seizures and dystonia as well as dementia. de Valk: None. Righi: None. Valo: A. Demchenko, Svetlana A. Conclusions: Pathogenic protein-truncating variants have been widely reported in heterozygosity manner, in adult-onset aneurysms. Massey: None. KalayciYigin: None. SNPs in the FKBP5 locus may affect its expression levels and have been associated with psychopathology. For 29% samples we didn't get the FISH result. In this study, we developed a machine learning-based framework, leveraging both genomic and tissue-specific transcriptomic features to predict previously unannotated 3'UTRs. We identify unannotated 3'UTRs associated with 1,513 genes across 39 human tissues, with the greatest abundance found in brain. Nale: None. Kelly: None. Consultant/Advisory Board; Modest; Amicus- Fabry. Grants: PI18/01233, FCHP unrestricted grant. Collaboratively combining data between institutes allows better understanding of mtDNA variants and is valuable for distinguishing pathogenic from benign variants. P15.051.C Whole genome sequencing in apparently balanced de novo chromosomal translocations in 10 patients with malformations and/or intellectual disability Irene Valenzuela Palafoll 1, Alejandro Romera-Lopez2, Anna M. Results: IC50 was calculated as 2.5 mM, at which cells were detected to undergo early apoptosis. First protein, a modified TFIIIA polypeptide to bind to the COVID-19 genome; second protein to be mounted on the surface of the cell alerting the immune system to B1.1.7 spike protein. Saetta National and Kapodistrian University of Athens, Medical school, Athens, Greece. The blood samples were processed for serum isolation, and exosomes isolation and miRNAs extraction were done using commercial kits. After multivariate analysis controlling for other confounding factors and comorbidities, HLA-A*11:01:01:01 [$P = 3.34E{-}03$, $OR = 3.41$ (1.50-7.73)], age at diagnosis [$P = 1.29E{-}02$, $OR = 1.04$ (1.01-1.07)] and sex at birth [$P = 8.88E{-}03$, $OR = 2.92$ (1.31-6.54)] remained significant. The syndromes of multiple congenital malformations (MVP) are a large group of clinical forms of hereditary diseases. Our study demonstrates the role of TLRs in AD pathogenesis. Plomp8, Reginald Bittner9, Mitja I. Results: Multiplex primers were designed using k-mer approach. Marafi: None. This underscores the importance of linkage disequilibrium patterns even for seemingly clear-cut loss-of-function mutations. Introduction: Assessing the clinical significance of copy gains is often challenging for genetic laboratories. Forner3, Raquel Cortes1 1Biomedical Research Institute Clinic Hospital - INCLIVA, Valencia, Spain, 2INSERM, U1016, I, Cochin Institute, Paris, France, 3Universitary Clinic Hospital, Valencia, Spain. However, congruent interpretation of a large number of genomic variants remains a key challenge in today's molecular genetics, which also stands true for HL. Taken together these evidences support the functional analogies between placenta and cancer. Results: We observed significant evidence of gene by sex interactions that account for ~1/3rd of ALS SNP heritability (likelihood-ratio test: $p = 0.0087$). Polyvalent mRNA to both neutralize Coronavirus genome and function as a COVID-19 B1.1.7 vaccine ▓ L.B. Scheiber II: None. Zagorac: None. Audoux: A. Materials and Methods: Using whole exome sequencing, we investigated samples from 52 CLL patients with a known clinical course and different scenarios of TP53 mutation expansions. Despite the recent progress of diagnosis and research, it remains a significant medical problem. Mariani: None. Interestingly, not all phenotypic features observed in the index have been previously linked to this MT-TL1 variant, suggesting either broadening of the m.3291T>C-associated phenotype, or presence of a co-occurring disorder. Oppert: None. A more in-depth analysis of the mutation revealed that the observed one base pair insertion creates a novel downstream in-frame start codon. Aldisi 1, Oleg Borisov1, Emadeldin Hassanin1,2, Andreas Mayr3, Peter Krawitz1, Carlo Maj1 1Institute for Genomic Statistics and Bioinformatics, University Hospital Bonn, Bonn, Germany, 2MeGeno S.A, Esch-sur-Alzette, Luxembourg, 3Institute for Medical Biometry, Informatics and Epidemiology, University Hospital Bonn, Bonn, Germany. Rodriguez-Antona: None. Kunze: None. Bartesaghi: None. The remaining variants were in genes: i) associated with syndromic forms of proportional short stature, KDM6A (Kabuki-syndrome; $n = 3$), NFKB2 (DAVID syndrome, $n = 3$), CUL7 (3M-syndrome, $n = 3$), and BTK ($n = 1$); ii) implicated in pituitary morphogenesis, PROKR2 ($n = 5$), IHH ($n = 5$); iii) extracellular matrix genes, ACAN ($n = 11$); or iiii) in genes encoding paracrine factors of the growth plate, NPPC; ($n = 2$) and NPR2 ($n = 3$). Galvão2, Cristina S. Droplet digital PCR (ddPCR) offers the potential for development of NIPD assays personalised to maternal variants, regardless of inheritance type, through relative mutation dosage. Conclusion: We present KidneyNetwork, a kidney-specific co-expression network that accurately predicts which genes have kidney-specific functions and can result in kidney disease. Methods: Prenatal sonography of a 44-year-old woman at 14 weeks of gestation (WG) showed tricuspid regurgitation, a small branchial cyst, single umbilical artery and retrognathia, at 19 WG additional heart, renal and brain anomalies. The estimated proportion of genetic risk borne by the X chromosome in this population is 70%. Coviello: None. 22q13.3 chromosomal region is, furthermore, reportedly involved in few cases of interstitial deletion beyond SHANK3 gene and rare cases of duplication. P08.050.D MYT1L-associated neurodevelopmental disorder: a clinical and molecular description of 37 new cases and literature review Juliette Coursimault 1, Anne-Marie Guerrot1, Michelle Morrow2, Bert Callewaert3, Sarah Vergult3, Laurence Faivre4, Frédéric Tran Mau-Them4, Ange-Line Bruel4, Estelle Colin5, Marine Tessarech6, Mathilde Nizon7, Benjamin Cogne7, Bertrand Isidor7, Cyril Mignot8, Diane Doummar9, Boris Keren8, Stéphanie Valence9, Delphine Héron8, Françoise Devillard10, Charles Coutton11, Marlène Rio12, Karine Poirier12, Elise Schaefer13, Bénédicte Gérard14, Gwenaël Le Guyader15, Frédéric Bilan15, Wendy Chung16, Rebecca Hernan16, Austin Larson17, Kelly Nori17, Sarah Stewart17, James Wheless18, Salima El Chehadeh13, Beth Pletcher19, Christina Kresge19, Margaret Helm20, Laurence Colleaux12, Anne-Sophie Alaix12, Jeanne Amiel12, Sophie Rondeau12, Roseline Caumes21, Thomas Smol22, Sabine Sigaudy23, Alexandra Afenjar8, Christine Coubes24, Christine Poitou25, Thierry Frébourg1, Pascale Saugier-Veber1, Gaël Nicolas1, François Lecoquierre1 1Normandie Univ, UNIROUEN, Inserm U1245, CHU Rouen, Department of Genetics and reference center for developmental disorders, FHU G4 Génomique, F-76000, Rouen, France, 2GeneDX, 207 Perry Parkway Gaithersburg, MD 20877, Gaithersburg, MD, USA, 3Center for Medical Genetics, Ghent University Hospital, Department of Biomolecular Medicine, Ghent University, Ghent, Belgium, 4Service de Génétique des Anomalies du Développement, CHU Dijon, Dijon, France, 5Department of Biochemistry and Genetics, Angers University Hospital, Angers, France UMR CNRS 6015-INSERM 1083 and PREMMI, Mitovasc Institute, Angers, France, 6Department of Biochemistry and Genetics,Angers University Hospital, Angers, France UMR CNRS 6015-INSERM 1083 and PREMMI, Mitovasc Institute, Angers, France, 7CHU Nantes, Service de Génétique Médicale, Nantes, France, 8APHP.Sorbonne Université, Département de Génétique, Groupe Hospitalier Pitié-Salpêtrière-Hôpital Trousseau, Centre de Référence Déficiences Intellectuelles de Causes Rares, Paris, France, 9APHP.Sorbonne Université, Service de Neuropédiatrie, Hôpital Trousseau, Paris, France, 10Service de génétique et procréation CHU Grenoble Alpes, Grenoble, France, 11Genetic Epigenetic and Therapies of Infertility, Institute for Advanced Biosciences, Institut National de la Santé et de la Recherche Médicale U1209, Centre National de la Recherche Scientifique UMR 5309, Université Grenoble Alpes, Grenoble, France, 12Department of Genetics, IHU Necker-Enfants Malades, University Paris Descartes, Paris, France, 13Service de génétique médicale, Hôpitaux Universitaires de Strasbourg, Institut de Génétique Médicale d'Alsace, Strasbourg, France, 14Laboratoire de Diagnostic Génétique, Hôpitaux Universitaires de Strasbourg, Strasbourg, France, 15Centre Hospitalier Universitaire de Poitiers, Service de Génétique, BP577, 86021, Poitiers, France, 16Columbia University Irving Medical Center, New York, NY, USA, 17University of Colorado, School of Medicine and Children's Hospital, Aurora, CO, USA, 18Division of Pediatric Neurology, University of Tennessee, Health Science Center, Memphis, TN, USA, 19Division of Clinical Genetics, Rutgers New Jersey Medical School, Newark, NJ, USA, 20Maine Medical Partners, Pediatric Specialty Care Genetics, Portland, ME, USA, 21Institut de Génétique médicale, Clinique Guy de Fontaine, Jeanne de Flandre, Lille, France, 22Pôle Biologie Pathologie Génétique, Centre de Biologie Pathologie Pierre-Marie Degand, Lille, France, 23Département de Génétique Médicale, Hôpital Timone Enfant, Marseille, France, 24Département de Génétique Médicale, Maladies Rares et Médecine Personnalisée, CHU Montpellier, Montpellier, France, 25Service de Nutrition, Hôpital de la Pitié Salpêtrière - AP-HP, Paris, France. Impaired function of α3 subunit V-ATPase leads to inappropriate extracellular acidification, osteoclast proliferation and unossified osteoid matrix. M.J. Jennings: None. The analysis was carried out either directly ex vivo on the cells of the fresh hippocampus or after culture of the primary cells in vitro under three conditions: (1) culture in neurospheres in non-adherent conditions for 19 days, (2) direct culture in GalC7 for 7 days and (3) culture in GalC7 for 7 days after 12 days in neurospheres; to complete culture days to 19 as in (1). Altner: None. Biallelic loss-of-function mutations in ZMPSTE24, however, have been associated with lethal restrictive dermopathy (RD), which leads to death within the first weeks of life. Rauf: None. P24.037.D Mitochondrial genetic determinants of nuclear gene expression variation among four European ancestries Josefina Lascano Maillard 1, Halit Ongen1,2, Emmanouil T. Disadvantages include a decrease in rapport-building, possibilities to interpret non-verbal cues, technical or language difficulties, inabilities to perform physical examination, less access to DNA sampling and privacy concerns. Rekik: None. Palmer: None. Hachmeriyan: None. In three cases, decreased transactivation activity could be explained by decreased DNA binding. Our pilot results confirm WES as a first-tier diagnostic test in the genetic evaluation of children with NDDs. Supported by Ministry of Health of the Czech Republic, grant nr. Thus far, almost 7000 diseases with a molecular basis are defined, of which almost 6000 single gene disorders, and around 4000 genes are known to harbor the pathogenic variants causal for the patient's phenotypes. Galosi: None. Kovalenko: None. Our results demonstrate the importance of considering overlapping phenotypes and differential diagnosis for genes' selection for NGS panels design. However, one lacked molecular confirmation and the other had limited clinical and molecular information.Case Study: We report a 13-year-old female with history of psychomotor delay most significantly speech, focal epilepsy, congenital heart disease, myopia, thin sparse hair with brittle nails, relative macrocephaly, short stature and coarse facial features. PGT-M was performed to select for N370S carrier embryos because of the reduced risk for PD, compare to 84GG carrier embryos. Three cases appear to involve an identically overlapping copy number gain (including a duplication, a triplication and a 6x amplification) with one of the breakpoints mapping to the structurally polymorphic cancer associated isodicentric 17q breakpoint cluster. The questionnaire explored the willingness of both groups to participate in distant genetic counseling (DGC), referral reasons and the way they would prefer to conduct DGC. 5 patients were carriers in compound heterocigosis and 4 of them were diagnostic at first year of life and could be studied the cosegregation. Methods: 183 untreated relapsing-remitting MS subjects have been studied. Fitremann: None. According to Orphanet data, its birth prevalence in Europe is 2.2 cases per 100,000 newborns. This work was supported by the Russian Science Foundation (grants no. Jensen2, Anja Ernst3, Henrik Okkels3, Rikke Christensen2, Thomas Balslev4, Lone Sunde1, Charlotte K. Conclusions: Our findings suggest that biallelic WDR11 variants in humans result in an overlapping but milder phenotype compared to Wdr11-deficient animals. Haudry: None. Results: The two unrelated males were born to consanguineous parents from Gafsa. Weerts1, Kristina Lanko 1, Francisco J. Two Secundum ASDs were found on echocardiography. P12.197.A Analysis of urothelial carcinomas by targeted RNA-Seq Jan Rehker, Marie-Lisa Eich, Sabine Merkelbach-Bruse, Reinhard Büttner University Hospital Cologne, Cologne, Germany. P06.026.C ZOEMBA: combining metabolomics and genomics data to solve the unsolved Machteld M. However, caution is needed regarding variant calling performance, particularly in the detection of (likely) pathogenic HGMD/ClinVar variants which should not be missed in clinical WGS. Hadzsiev: None. Recognition of microbial patterns, cytokine and acute phase responses, hemostasis features and alterations in plasma lipid and calcium profile all have been reported to affect pathogenesis and clinical course of IE. M.E. Koko: None. Berg: None. Results: We identified a synonymous GNAS variant NM_001077488.2:c.108C>A / p.(Val36=) present in the affected members with IPPSD2 phenotype. FMP predicted 107 (70.9%) B variants in the cytoplasmic, 10 (6.6%) in transmembrane, and 34 (22.5%) in extracellular domains. Lildballe: None. Introduction: Oligodontia-colorectal cancer syndrome (OMIM 608615) is an autosomal-dominant disease, which prevalence according to Orphanet is T, p.(Pro30Leu) LP GDF1 c.681C>A, p.(Cys227*) P PS, VSD Y Y EP300 c.3739T>C, p.(Cys1247Arg) LP Truncus arteriosus N N CRELD1 c.959delA, p.(Gln320Argfs*25) LP Tetralogy of Fallot N Y GLI3 c.642delC, p.(Met215*) LP CRELD1 c.1103T>A, p.(Leu368*) LP Truncus arteriosus N N HAND1 c.410_411delinsA, p.(Arg137fs) P PS, VSD N N JAG1 c.1278del, p.(Cys427fs) P AVSD Y Y MYH11 c.4882A>C, p.(Lys1628Gln) LP BAV, TAAD Y N GDF1 c.681C>A, p.(Cys227*) P BAV N N FOXC2 c.1402dupG, p.(Glu468Glyfs*?) LP HLHS, BAV Y Y PTPN11 c.1505C>T, p.(Ser502Leu) P HLHS N Y PTPN11 c.179G>C, p.(Gly60Ala) LP ASD Y Y ACTC1 c.904T>A, p.(Ser302Thr) LP HLHS, incomplete AVSD, primum septum defect, narrower AoV, hypoplasia aortic arc with COA Y Y PTPN11 c.1529A>C, p.(Gln510Pro) P HLHS with mitral valve atresia, hypoplastic aortic arch, PDA ASD N N NOTCH1 c.3177del, p.(Val1060fs) P M.M. Hitzert: None. Elmslie: None. We assessed the participation of contiguous genes never associated with human diseases before, by using the data-mining software Manteia to compare with phenotypes observed in murine knockout models. Two quantitative heritable and polygenic quantitative traits were considered, namely height and LDL cholesterol levels. Thirteen patients lack variants in analyzed genes.According to our study, congenital glaucoma could be associated frequently with genes that are usually linked to anterior segment dysgenesis including Axenfeld-Rieger syndrome.Carried out within the state assignment of Ministry of Science and Higher Education of the Russian Federation, supported in part by RFBR grant (No. 19-015-00122). We observed a significant enrichment of DNM-hits for motif TFAP2A in nsCL/P, and identified ATF3, MSC and HES5/7 as potential TF candidates. Introduction: Congenital heart diseases are one of the most common multi-factorial fetal abnormalities caused by a complex of endo- and exogenous factors. Spasova1,2, Boryana Gerasimova2, Olga S. In human cells, MDC1 loss promotes unrestrained resection of DNA ends, as indicated by increases in the number and intensity of RPA-coated ssDNA foci in a process that is dependent upon ATR and CtIP. Ossowski: None. Core clinical symptoms entail intellectual disability, muscular hypotonia, dysarthria, gait abnormalities, peripheral neuropathy and autonomic dysfunction. Simard: None. Chae: None. Furthermore, such gains may illuminate SV mutagenesis mechanism(s) and provide insight into potential PTLS contributing genes other than the 'driver RAI1 gene'. N.O. Yurkina: None. P09.047.D PIGG variant pathogenicity assessment reveals novel features within nineteen families Camille Tremblay-Laganiere 1, Reza Maroofian2, Thi T. Kornetov2, Maria G. Exome data were interpreted in agreement with local practices. Conclusions: Our findings identify a new function for SMN in the re-establishment of the proper nucleolar organization after DNA repair. Detailed phenotype and variant data and were gathered. A.C. Alves: None. Methods: Paired samples of colorectal polyps, tumors and/or mucosa were analyzed using a custom NGS hereditary-cancer panel. V.E. Fernández-Montaño: None. Tsepilov: None. At least 93 (63.6%) of diagnosed patients had a disorder that has targeted treatment, evidence for optimizing treatment, or on-going clinical trials. Materials and Methods: A family with an insertional translocation (inherited in both balanced and unbalanced forms) is presented. The variant was identified in 21/5495 healthy controls. Procaccio: None. Alvarado: None. Relatives of the participants were asked to complete a structured online questionnaire, including socio-demographic and clinical data. Since the initial description of the disorder and families, several new patients were diagnosed, adding more evidence of the clinical manifestations. Our aim was to estimate whether genetic predisposition to a wide range of heritable traits was associated with the estimated genetic predisposition for the COVID-19 outcomes from the January 2021 release of the Covid19 Host Genetics Initiative. Gershon-Naamat: None. However, the specific consequences of these mutations at the molecular/cellular level, including the cell types/developmental stages that are crucially relevant for the phenotype, remain unclear. The suspected diagnosis was compared to the molecular findings. Results: We identified 3 loci that significantly associate with CD68+ macrophages and ACTA2+ SMCs, pT: p.Val1045Leu, NM_016937.4: c.1436C>T: p.Thr479Ile, NM_003935.5: c.2018T>A: p.Leu673Gln novel heterozygous variants were detected in the MACF1, POLA1 and TOP3B genes, respectively, and the homozygous SLC13A5 gene: c.425C>T: p.Thr142Met mutation. Pereira 1,2, Andreia Santos3, Eugenia Cisneros4,5, Intissar Anan6, Marina S. Here we report a case of a boy with elevated CK and mosaic DMD mutation. Parkinson's disease (PD) is a common neurological disorder, hallmarked by progressive motor and autonomic dysfunctions and cognitive decline, with a typical onset after the age of 60. This study aimed to investigate the effect of different numbers of SRCR-repeats variation on transcript length and protein length. For 15.6% of the cohort patients, we observed a direct potential for the redirection of care with targeted therapy, tumor screening, medication adjustment and monitoring for disease-specific complications. We aim to identify challenges and pitfalls in PGT for NF1. The development of molecular techniques and the stasis of cytogenetics have led to underestimate the causative role of structural micro-rearrangements. Students' self-reported certainty about choices to report was lower for high uncertainty vignettes ($M = 79.99$) than for low uncertainty vignettes ($M = 90.33$), p 80%), which was also reflected at the mRNA level. Rojano: None. Receptor densities (protein expression levels) were quantified by autoradiographic analysis. Material and methods: Analysis of POLE/D1 exonuclease-domain pathogenic variants reported in the literature (15 germline variants in 59 independent families) and in publicly available databases (18 somatic variants in 77 proofreading-deficient tumors; source: TCGA), was performed. Deelen: None. M.E.H. Simon: None. Cole: None. Saraçoğlu 1, Yeliz Güven2, Sermin Dice Aksakal2, Tuğba Kalaycı3, Umut Altunoğlu4,5, Zehra Oya Uyguner6, Serpil Eraslan5, Esra Börklü-Yücel5, Hülya Kayserili Karabey4,5,7 1Koç University, Graduate School of Health Science, Cellular and Molecular Medicine, İstanbul, Turkey, 2İstanbul University, Faculty of Dentistry, Department of Pedodonty, İstanbul, Turkey, 3İstanbul University, Faculty of Medicine, Department of Internal Medicine, İstanbul, Turkey, 4Koç University, School of Medicine, Department of Medical Genetics, İstanbul, Turkey, 5Koç University Hospital, Genetic Diseases Evaluation Center, İstanbul, Turkey, 6İstanbul University, Faculty of Medicine, Department of Medical Genetics, İstanbul, Turkey, 7Koç University, Graduate School of Health Sciences, İstanbul, Turkey. Secondary findings were reported in 37 patients (7.4%). Its disruption may indicate a reproductive failure revealed as decreased quality of seminological parameters and/or fertility problems. Histology showed 2 papillary and 2 follicular TCs. Conclusions: Multinodular thyroid disease and thyroiditis are common findings in PHTS patients. Candidate variants were validated by Sanger sequencing in patients and segregation analyzes were performed in the family members that can provide samples. Methods: Development of the tool was based on interviews with women/their partners ($N = 42$) following prenatal CMA

to explore their experience with parental choice. Among the de novo cases, mosaicism could explain the typical PJS cases for which no pathogenic variant is identified in the STK11 gene. The Barcelona Institute for Science and Technology, Barcelona, Spain, 3Erasmus University Medical Center, Department of Clinical Genetics, Rotterdam, Netherlands, 4IMIM - Hospital del Mar Medical Research Institute, Barcelona, Spain, 5Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable (CIBER-FES), Madrid, Spain, 6Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA, 7Channing Division of Network Medicine, Harvard Medical School, Boston, MA, USA, 8Institute of Evolutionary Biology (CSIC-UPF), Department of Experimental and Health Sciences, Universitat Pompeu Fabra, Barcelona, Spain, 9Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain, 10Present address: H. Our genetic analysis therefore supports the importance of gene dosage measurement with NGS-based CNV analysis, Karyotyping, and FISH analysis for identifying causes of choroid plexus hypertrophy. P24.045.D Genetic association analyses identify links between pelvic prolapse (PP) and connective tissue biology, cardiovascular and reproductive health Natàlia Pujol Gualdo 1, Maarja Lepamets1, Kristi Läll1, Riikka Arffman2, Terhi Piltonen2, Reedik Mägi1, Triin Laisk1 1Estonian Genome Centre, Institute of Genomics, University of Tartu, Tartu, Estonia, 2PEDEGO Research Unit, Department of Obstetrics and Gynecology, University of Oulu, Oulu, Finland. L.S. Matsa: None. Results: Mutations in TP53 gene were revealed in four patients (4/18). Conclusions: Cosegregation studies could be useless in those families with small number of affected relatives. We evaluated the driving disease combinations at identified loci using Bayesian information criterion (BIC). By immunocytochemistry, we detected an increase of intracellular vesicular β1 integrin which strongly co-localized with RAB5, RAB21 and EEA1. Conclusions: Our results suggest that specific variants in the HLA-DRB1 gene are associated with reduced risk of PD, providing additional evidence for the role of the immune system in PD. Savvidou: None. Heiner: A. Medvedieva1, Ludmila I. Ourani: None. Real-Time PCR (RT-PCR) tested positive for a high concentration of SARS-CoV-2. The aim of the present study is to analyse and compare the expression patterns of miRNAs in ADC and SCC samples. Twenty-two genes belonging to CYP 1, 2 and 3 families were sequenced among others. Introduction: Tobacco smoking is one of the major risk factors for many chronic diseases and is the leading cause of preventable death in the world. C.G. Salter: None. Cedeno: None. The 135-gene test included sequence variant, CNV, and targeted noncoding variant analysis. Magini: None. Scarano: None. Introduction: Methylmalonic acidemia/aciduria (MMA) is a genetically heterogeneous inherited disease from the group of organic acidemias. McReynolds, Manfred Boehm, Alexandra F. G.K. Tolibova: None. Conclusions: Exome sequencing identifies potentially causative germline variants underlying the susceptibility to SPS; however, the preliminary data indicate considerable genetic heterogeneity. Ciuca: None. Filtering tools enable variant prioritization. M.P. Bellazzi: None. Moreover, use of L-dopa and duration of the disease had no effect on D-loop methylation levels in PD patients. Arabia: None. Milone: None. In 1000-Genomes data, we found stronger patterns of negative selection on ID and skeletal disorders than on other recessive disorders. Chan, S Sivapatham, H B. Low IgA levels were detected in 8/44 patients (18.18%), low CD8 T cells in 13/35 (37.14%). Narravula: None. Lung had the highest number of mutations with PCDH9 most frequently mutated (~6% of cancer samples). Mutations in α (HADHA) or β (HADHB) subunits can result in general TFP deficiency, while the HADHA p.Glu510Gln mutation accounts for isolated 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency. Ockeloen1, Christopher Richmond8, Eva M. Intratumoral heterogeneity and clonal variability is one of the central problems in clinical oncology, being the reason for the development of resistance to therapy and relapses. Conclusions: This experiment demonstrates how PacBio HiFi data analyzed with pbAA simplifies targeted disease allele identification. Tsepokina: None. P14.005.B Cytogenetic profile of newly diagnosed patients with acute myeloid leukemia - a single centre retrospective study Dinnar Yahya 1, Tsanka Ruseva2, Mari Hachmeriyan1, Lyudmila Angelova3, Ilina Micheva1, Trifon Chervenkov1 1UMHAT "St. Marina", Varna; Medical University "Prof. Funding: NKFIH K128736, FK134355 J. Westenberger: None. Mostly, an underlying cause is not identified, but MLID may be associated with biallelic pathogenic variants in ZNF57 or in maternal effect genes (MEGs) such as NLRP2, NLRP7, NLRP5, PADI6 and KHDC3L. A genetic diagnosis was established in 210 patients (36 genes): a molecular diagnostic yield of 24.7%. WES detected paternally inherited heterozygous variant c.663+1G>A TBX5 (NM_181486.4). Periodontal Ehlers-Danlos syndrome (pEDS) is a rare condition caused by autosomal dominant pathogenic variants in the C1R and C1S genes, encoding subunits C1R and C1S of the first component of the classical complement pathway. Materials and methods: Total RNA was extracted from normal and tumor tissue of gastric cancer patients using Trizol. Methods: Massively parallel sequencing (Illumina, USA) was performed in both cases, followed by Sanger DNA sequencing in order to verify detected variant segregation in available first-degree relatives. Vogric: None. Azar: None. MS was calculated as the total number of impaired senses. Neuzillet: F. P04.061.B Identification of rare variants for nonsyndromic cleft lip with/without cleft palate in a cohort of multiplex families Annika Scheer 1, Fabian Brand2, Julia Fazaal1, Nina Ishorst1, Peter M. Moldovan2, P. Method: A total of 1,150 publications were systemically reviewed. Fadda: None. Goldenberg: None. S.C. Previtali: None. Its etiology is diverse, however, genetic factors are significant. Methylation-specific polymerase chain reaction (MSP-PCR) was used to determine the methylation status of MB-COMT promotor, DRD2, and NR3C1 gene from DNA material. Ludwig1 1Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Bonn, Germany, 2FASTGenomics, Comma Soft AG, Bonn, Germany. The analysis of the expression of candidate genes in TRAF7-KD fibroblasts showed promising results for ANGPT1 and CASK, found downregulated in patients but significantly upregulated in TRAF7-silenced cells. Zieger1, Julia Schröder1, Magdalena Laugsch2, Kerstin U. P24.010.A Reimagining the metabolic syndrome: A composite complex trait Mads Engel Hauberg Department of Clinical Genetics, Odense University Hospital, Odense C, Denmark. Additionally, albuminuria and serum urea after a 12-month treatment of mice with 4-PBA have not reached the high values demonstrated by the non-treated AS mice (p-value A (rs28934578), their mother had breast cancer at age 35. Bae: None. Developing personalised therapeutics and associated diagnostics requires interdisciplinary teams, including oncologists, geneticists, immunologists, pathologists etc. Sarra: None. Twelve focus groups were conducted in six cities in the Punjab province of Pakistan: six with relatives of children with βeta thalassaemia major (β-TM) and six with HCPs affiliated with the government funded ‘Punjab Thalassaemia Prevention Project’ (PTPP). In 3 patients have compound heterozygote SNV. For each gene, our aim was to cover regions of pathogenic mutations in a single contiguous sequence or set of sequences that can be assayed in a single reaction. Marcellus: None. Demuth: None. Brain abnormalities were reported in 8/10, consistently including dysgenesis or thickening of the corpus callosum (8/8). Materials and Methods: We performed a two-sample Mendelian randomization (MR) analysis using two pairs of publicly available genome-wide association study (GWAS) summary statistics for Europeans from UK Biobank (Gene ATLAS, N = 452,264) and FinnGen (N = 176,899). Genetic studies in painful PN (PPN) revealed that Voltage Gated Sodium Channels (VGSCs) genes are involved in pain amplification. Personality traits: anxiety and impulsiveness with Conner’s test, pursuit of high (PH) and low (PL) intensity pleasure with Temperament in Middle Childhood Questionnaire (TMCQ). Ruxolitinib is an orally available receptor tyrosine kinase inhibitor that targets JAK1 and JAK2. Splice-prediction algorithms could be added to the bioinformatic pipelines for MPS data in routine analysis to improve the detection of such variations. Nicolas Rocamora: None. The diagnostics is highly challenging due to the heterogenic genetic background. Nampoothiri: None. In light of this discovery, we aimed to evaluate the impact of SORD mutations in a cohort of unsolved individuals with CMT. Materials and Methods: The association study was performed on 127 patients and 254 controls after obtaining written informed consent. Almadani: None. We describe a girl who presented with body asymmetry, plagiocephaly, microcephaly, myelomeningocoele, cradle cap, digital and skeletal anomalies, hypertelorism and optic nerve colobomas during the neonatal period. Terczyńska: None. Materials and Methods: Semi-structured interviews were carried out with 25 parents of 15 children with a postnatal diagnosis of DS aged 4-12 years. The Solve-RD project has enabled ITHACA data sharing and clinical patient selection at a pan-European level. Romaniello: None. P13.025.B Role of hypomorphic variants in variable expressivity of Noonan syndrome Viviana Tritto 1, Eleonora Mangano2, Maria T. It is necessary to regulate in detail the issues of gene editing in relation to humans. Pachuliia1, Nataliya O. Scocchia: A. Pachota: None. The disease manifested by high temperature, hepatomegaly, acholic stools. Here, we present an approach to identifying new genetic determinants of OC predisposition by analyzing exceptional responders to platinum-based therapy. Mintz28, Reymundo Lozano29, Jennifer E. The combined results can be described as an integrative polygenic score (IPGS) computed as: (nmildness-nseverity) +F (mmildness-mseverity) where n is the number of common driver polymorphisms, m is the number of rare driver variants and F is a factor for appropriately weighing the more powerful rare variants. Genetic diagnosis is important in children presenting with infantile high myopia, which can be the presenting sign of a degenerative ocular disorder. Immesoete: None. Identifying these factors is crucial in personalized treatment approaches. Arkadir: None. SETD1B encodes a lysine-specific histone methyltransferase that methylates histone H3 at position lysine-4 (H3K4me1, H3K4me2, H3K4me3) and thereby is involved in the regulation of gene expression. Fino: None. Tailored molecular testing approaches for difficult-to-sequence genes contributed to 12.9% (36/279) of diagnoses (confirmed with orthogonal methods). Verkarre: None. The development of algorithms to predict which patients are most likely to participate may further improve overall engagement in this genomic screen. Seppala2, Lotta Koskinen2, Juha Koskenvuo2, Tero-Pekka Alastalo2 1BioMarin Pharmaceutical Inc, Novato, CA, USA, 2Blueprint Genetics, San Francisco, CA, USA. S.C. Credendino: None. We observed that some features seems to have a higher frequency in our cohort compared to those of the literature, notably 2nd ray clinodactyly and Angel Shaped Phalango-Epiphyseal Dysplasia, joint laxity, various dental abnormalities, premature osteoathritis and hip disorders (mainly coxo-femoral dysplasia). Prenatal exome sequencing using DNA derived from amniocentesis and from both unrelated parents identified compound-heterozygosity for the variants c.498G>A, p.[(=),0?] and c.302C>T, p.(Pro101Leu). Yoo: A. 33% of patients who are resistant to therapy TKI have loss-of-function variant in the ASXL1 and DNMT3A genes, with 25% only in the ASXL1 gene, and 8% in ASXL1 and DNMT3A. Pelacani: None. P11.047.A Evaluation of the diagnostic rate in children with dysmorphic features - one genetic center experience Milena Stoyanova 1,2, Mari Hachmeriyan1,2, Mariya Levkova1,2, Valentina Miteva1,2, Lyudmila Angelova1 1Medical University, Varna, Bulgaria, 2University Hospital Saint Marina, Varna, Bulgaria. Karyotyping (GTG- and C-banding) and FISH-analysis (fluorescence in situ hybridisation) with a CEP 9 probe (9p11-q11 Alpha Satellite DNA) revealed an additional marker chromosome, which was identified as an additional isodicentric chromosome 9p. Decker: A. Seixas: None. Martina Bebin5, Stefanie Beck-Wödl6, Gea Beunders7, Natasha Brown8, Melanie Brugger9, Theresa Brunet9, Philippe M. The data was collected reviewing clinical records. Our data demonstrate that CS-associated HRASGly12Ser interferes with RIN1-RAB5 mediated endosomal sorting of integrins and, thus, adhesion-dependent processes. He also had mild intellectual deficiency. However, even within European-centered GWAS data, there are local subpopulations significantly under-represented in these studies. To unravel the underlying regulatory network, we are establishing a combined approach of circular chromosome conformation capture (4C) and ChIP-seq in iPSC-derived hNCCs, and first results will be presented at the conference. Uterine lavage is a non-invasive technique sampling cells shed into uterine cavity by EC and OC. Conclusions: Families are positive about WES, however we identified several challenges pertaining to timing, consent and follow-up. Miclea: None. Visualization of genetic distances between locations and periods indicated a decrease of reduced genetic distance over time between locations but was found to not be statistically significant with formal testing. D’Ambrosio: None. Together these findings identify MNS1 alterations as a potential under recognised cause of male infertility and highlight the importance of including MNS1 on gene testing panels globally. Background: Keipert syndrome is a rare X-linked disorder caused by pathogenic variants in GPC4gene. Philippe: A. Winczewska-Wiktor: None. Finally, we identified HPV infection by RT-qPCR. Servicio de Pediatría. The clinical profile and the genetic heterogeneity of RASopathies could make choosing between panel testing and WES analysis difficult. Agrawal21,22, Eleina England23, Jill A. Domínguez: None. Results: The study cohort consisted of 625 Hispanic/Latino subjects with a mean age 46.0 ± 13.5 years and 57% were male. Irene Novo, Eugenio López-Cortegano, Armando Caballero Centro de Investigación Mariña, Universidade de Vigo, Vigo, Spain. Stylianou: None. Few translocations involving other chromosomes have been reported. Introduction: North Carolina macular dystrophy (NCMD) is an autosomal dominant, congenital disorder affecting the central retina. Schutte: None. Using different methods we observed statistically significant differentiation between periods in general, between locations within both the historical periods and present day and between periods within locations. Freixo1, Jorge Sequeiros1, Jorge Oliveira1 1CGPP-IBMC/I3S, Porto, Portugal, 2Serviço de Neurologia, Centro Hospitalar e Universitário de Coimbra, EPE, Coimbra, Portugal, 3Serviço de Neurologia, Centro Hospitalar de Vila Nova de Gaia/Espinho, EPE, Vila Nova de Gaia, Portugal, 4Serviço de Genética Médica, Centro Hospitalar Universitário de São João/Faculdade de Medicina da Universidade do Porto, Porto, Portugal, 5Centro Hospitalar Universitário do Porto, Hospital de Santo António, Porto, Portugal. Those irregularities in epithelial thickness profiles in KTCN were reflected in transcriptomic profiles. Except for the detection of a new gene mutation (TP53 p.Lys132Glu, 0.19%) in August 2018, the monitoring results of liquid biopsy are all normal in October 2018, April 2019, November 2019, and April 2020. Lebl: D. Differential gene expression analysis across time points was performed using DESeq2 v1.30.0 and pathway analysis of differentially expressed genes within each cell line was performed using clusterProfiler v3.18.1. Results: We identify genes uniquely expressed within both the differentiated and undifferentiated states of each cell line, as well as a core set of genes that characterise the change in RNA abundance associated with PMA-induced monocyte-to-macrophage differentiation. Moilanen: None. Babaei: None. Results: It was shown that 451 (56.3%) women are ready to undergo IPT with a high risk of fetal CA, 39 (4.8%) - will not do the procedure, 281 (35.1%) were undecided, 29 (3.6%) did not answer the question. Fernández-Cadenas: None. Tlemsani: None. D’Aurizio: None. Biallelic ALDH1A3 variants are responsible for 11% of recessive AM cases, mostly described in consanguineous families, and present severe bilateral AM with variable neurodevelopmental anomalies. L.H. Ngu: None. Guerrot: None. M.G. Filippova: None. Alves1 1Department of Clinical Genetics, Erasmus University Medical Centre, Rotterdam, Netherlands, 2Department of Pediatric Surgery, Erasmus University Medical Centre - Sophia Children’s Hospital, Rotterdam, Netherlands. Result, new perspectives: All collected cases resembling a POGZ-related disorder (n = 13; 8 male) presented with ID (from mild to severe), a global DD, usually exhibited behavioural impairments and, in five cases, a diagnosis of ASD. Newbury: None. Benetti*: None. Wyrwoll 1,2, Manon S. Selvatici: None. Five patients had feeding difficulties during infancy; one had a suspected Pierre-Robin sequence, another had a velar cleft palate. Scheiber II, Lane B. Torroni: None. P16.031.B Transthyretin, Retinol-binding protein, retinol and T4 circulating levels in the Mallorca population of TTR V30M carriers Eugenia Cisneros-Barroso, Juan González, Adrián Rodríguez, Tomás Ripoll-Vera, Inés Losada Fundació Institut d’Investigació Sanitària Illes Balears – IdISBa, Spain, Spain. In addition, Transcriptome analysis (RNASeq) was also initiated in 22 cases. P02.041.A Cone-related transcriptomic profiles in Keratoconus corneal epithelium Katarzyna Jaskiewicz 1, Magdalena Maleszka-Kurpiel2,3, Malgorzata Rydzanicz4, Justyna A. Gruchy: None. P12.072.D Identification of the R882H mutation in DNMT3A by a restriction test in patients with hematologic neoplasms Elizaveta Kulaeva 1, Pavel Lipilkin2, Tatyana Lipilkina3, Elena Mashkina1 1Southern Federal University, Rostov-on-Don, Russian Federation, 2Rostov State Medical University, Rostov-on-Don, Russian Federation, 3Don State Technical University, Rostov-on-Don, Russian Federation. Although previously reported heterozygous carriers are asymptomatic, it has been recently described that the carrier frequency of AAGGG repeat expansions is up to 21.2% among patients with late-onset ataxia. A disruptive variant in KIF4A has been described to cause X-linked intellectual disability and epilepsy. P09.025.B Contribution of compound heterozygous CACNA1H mutations in autism spectrum disorder susceptibility Marta Viggiano 1, Cinzia Cameli1, Annio Posar2,3, Maria C. The aim of this study was to define salivary extracellular vesicle-derived epigenetic biomarkers suitable for type 2 diabetes diagnosis. Lemke: None. Stroeks1, Debby M. Schleit: None. Aguirre Rodriguez: None. Methods: As alterations of DPY19L2 gene represent the main cause of globozoospermia in human, we first screened for DPY19L2 molecular defects in a cohort of 10 patients of African and European origin, diagnosed with complete or partial globozoospermia. Di malta: None. Dapia: None. Backgrounds: The proportion of assisted reproductive technology (ART)-conceived livebirths of patients with imprinting disorders (IDs) is higher than that of the general population. Carriers of PVs in DNA repair genes (18/212 patients) showed a statistically significant lower asbestos exposure than non-mutated patients (p = 0.0001). Conclusions: A few questions remain unanswered regarding this case. P08.029.C Next generation sequencing of a genes panel for the study of Mexican patients with global developmental delay María de la Luz Arenas-Sordo 1,2, Paola Linares-Mendoza1, Karina Peñuelas-Romero1, Javier Martínez-Martínez1 1Instituto Nacional de Rehablitacion, Mexico City, Mexico, 2Universidad Nacional autónoma de México, México City, Mexico. Akbari: None. Introduction: Autism Spectrum Disorder (ASD) is a complex neuropsychiatric disorder with a strong genetic component. Among the 3 known variants, a deletion causing truncation (c.381delA resulting in p.Val128Ter) was identified in 13 patients. Vermeer2, Ludolf G. This aberration can arise by various causes such as congenital connective tissue disorder (CCTD), injury or inflammation and is accompanied by bicuspid aortic valve, arterial hypertension and atherosclerosis. Nurm: None. In this context, several methods have been described that use unique molecular identifiers (UMIs) to analytically remove NGS errors. Introduction: Disorders of sex development (DSD) comprise a heterogeneous group of congenital conditions associated with atypical development of internal and external genitalia. We present four patients clinically or in newborn screening (NBS) conspicuous for CF with very rare or unknown CFTR variants. Marin Suarez: None. Longer telomeres in TE may be linked to its crucial role in implantation and subsequent placentation, both accompanied by a high mitotic activity. Mortier: None. Sistermans: None. Conclusions: Although nurses realized the importance of genetics/genomics to their practice, and genetics is part of the Israeli nursing core-curriculum, we found disappointingly low levels of knowledge and performance of genetic skills in nursing practice. Conclusion: Here we report the second patient with congenital microcephaly caused by two heterozygotes variants in KATB1 gene. However, cochlear implantation cannot be considered as a treatment (disturbance in noise, social difficulties and professional integration...). Introduction: Chromosomal instability is one of the hallmarks of cancer and usually detected by expensive and time-consuming array CGH or low coverage whole genome sequencing. Sayegh Martin: A. All studies have a main trait (the variable under investigation), but many also include a background trait shared by all study participants (e.g. “Allergic rhinitis in asthma”). Because of the high risk for chromosomal abnormalities in the fetus, assisted reproduction with PGT-A was recommended and performed by Next Generation Sequencing after Whole Genome Amplification using Veriseq (Illumina) protocol. P15.032.D Introduction of a walk-away automated Roche NGS workflow solution: Integrated KAPA Library Preparation, KAPA Target Enrichment and the AVENIO Edge instrument Persis Wadia, Joshua Lefkowitz, Edwin Malfarta, Arrezo Moghaddasi, Smriti Sharma, Benjamin Morck, Patrick Ton, Tim Williams, Michael Pintor, Jennifer Dasgupta, Arash Fararooni, Arafat Al-Ariemy, Bill LaRochelle, Pierre-Luc Janvier, Neda Razavi Roche, Pleasanton, CA, USA. To search for the epigenetic mechanisms contributing to disease, we explored the DNA-methylation profile of OAVS individuals. The smallest region of overlap for the phenotype of brain malformations and intellectual disability is refined to a segment of 325 kb in 6q27, comprising the protein coding genes DLL1, PSMB1, TBP and PDCD2. Makhaldiani: None. Association analyses included genetic predisposition to COVID-19 outcomes as the variables of interest. Only one patient was homozygous for -α3.7gene deletion. WGS Trios from 11 previous cases were uploaded to the software and the results analysed. Rodríguez-Nóvoa1 1Metabolic Disease Laboratory, Genetic Department. Results and Conclusions: According to our results, in 8 of 93 samples (8,6%) trisomy 8; in 43 of 93 samples (46%) (38 of them large deletion or monosomy 13) deletion of 13q; in 13 of 93 samples (13%) loss of TP53 were detected, whereas monosomy 7 in none. Material and Methods: We present a 7-months-old girl who was born after a complicated pregnancy at 37 weeks of gestation (screening of first trimester of high risk and anormal Doppler, aberrant subclavian artery and intrauterine growth restriction in ecography). Risk category according to BSG guidance was assigned de novo. Targeted NGS analysis was performed with a customized panel including 500 genes related with metabolic diseases. Lu: A. Data were analyzed prospectively from January 2017 to December 2020. Arg783His and p.Val1213Met in MYH7, a frameshifting p.Lys1065Glnfs*12 and a splicing c.1458-1G>A variations in MYBPC3. 21 samples gave non informative results (T; c.432T>G, p.(Phe144Leu) and c.749C>A, p.(Ala250Glu). P17.006.A Leveraging auxiliary data from arbitrary distributions to boost GWAS discovery with Flexible cFDR Anna Hutchinson 1, Guillermo Reales2, James Liley3, Chris Wallace1 1MRC Biostatistics Unit, University of Cambridge, Cambridge, United Kingdom, 2Cambridge Institute of Therapeutic Immunology & Infectious Disease (CITIID), University of Cambridge, Cambridge, United Kingdom, 3University of Edinburgh, Edinburgh, United Kingdom. Robert: None. Hereditary cancer-predisposing syndromes were found in 31 participants (2,5%), among them 12 individuals in the questionnaire indicated personal or family cancer history. In order to establish the effect of reported mutations on splicing, a functional analysis is required. Materials and Methods: Genome-wide linkage analysis combined with whole exome sequencing were performed to identify disease-causing variants. Roshcheniuk2,4, Vitalii M. Lancet: B. It encodes a magnesium transporter located in plasma membrane and early endosomes, implicated in neuronal development and maintenance. Altogether, this will enable us to discover novel genes, phenotypes and evaluate the usefulness of integrated multi-omics data in clinical practice. Most HON patients present mutations in the mitochondrial genome and OPA1. Conclusion: Men with the HFE p.C282Y homozygous mutation developed substantially more marked brain iron deposition in dementia relevant brain areas and were more likely to be diagnosed with dementia during follow-up in hospitalization data. Introduction: Over the past decade, telomere biology has become an important topic in the field of human reproduction. Alfadhel: None. Other; Modest; BioMarin Pharmaceutical Inc, Sanofi, Takeda. Grossmann: None. All variants are absent from the gnomAD database. Zaynitdinova, Anna G. Conclusion: In the current study we have shown that MSC-derived exosomes alter the EMT in TNBC cell lines and that these alterations take place in a spatial-directed manner. Ratajska: None. Carda: None. It provides a broad diagnostic spectrum, from NIPT to hereditary cancer solution, from hemato-oncogenetics to molecular characterization of solid tumors, and coordinates the outsourcing of specific genetic testing to external partner centers when needed. Galli: None. van Gijn, Cleo C. Prat-Planas: None. By means of interactome and functional analysis, we have molecularly characterized two missense variants, providing new insights on the pathomechanistic consequences of TLK2 mutations on intellectual disability and neurodevelopmental disorders. We observed no genotype-phenotype correlation within those cases. Here, we assess the pertinence of UPD-events in the context of rare disease diagnostics. Adham: None. Zinchenko Research Centre for Medical Genetics, Moscow, Russian Federation. Each of the families had at least three affected family members over at least two generations. For the whole cohort genome- and epigenome data will be collected using the microarray technology (Illumina). In each family a heterozygous SCN5A mutation has been identified from peripheral blood extracted genomic DNA. All rights reserved., Seattle (WA). The Telethon Undiagnosed Diseases Program (TUDP) is a multicentric Italian national program with the objective of studying a broad spectrum of rare paediatric-onset monogenic disorders, characterized by severe multisystem manifestations, neurological involvement, and dysmorphic features. Pias: None. McLaughlin1 1Smurfit institute of genetics, Trinity College Dublin, Dublin, Ireland, 2Department of Neurology, Brain Centre Rudolf Magnus, University Medical Center Utrecht, Utrecht, Netherlands. Moscatelli: None. Clinical validity of ddPCR assays for treatment monitoring was shown, as ctDNA quantities were associated with response or resistance to chemotherapy in 7/7 patients. Peruga: None. Normanno: B. Almassy: None. Oliva: None. Auburger: None. Introduction: Non-syndromic hearing loss is a genetically heterogeneous sensory disorder. Results: NGS analysis of patient`s DNA revealed two rare compound heterozygous variants in NPC1: typical loss-of-function c.2196dup (p.Ala732fs*30) mutation and c.2727C>T (p.Cys909=) variant of unknown significance. Kaygisiz: None. Tabano: None. Material and methods: Direct sequencing was performed in a cohort of 8 patients with PM and 9 of their clinically healthy relatives from 2 unrelated families in central Tunisia. Ramsey: None. P05.025.C Identification of a novel TPM1 variant causing hypertrophic cardiomyopathy in an Indian family Prabodh Kumar 1, Ganesh Paramasivam2, Tom Devasia2, Mukund Prabhu2, Maneesh K. Dysmorphic findings of the patient included microcephaly, bitemporal narrowing, high palate, dental malocclusion, maxillary hypoplasia, and a prominent auricle. Participants identified various strategies for facilitating family communication but noted that constraints on time and resources hindered their ability to support patients with disclosure. Both variants were already reported in patients with GM1-Type II, leading to 3-5% of residual enzyme activity. Notably, the absence of family history does not reliably exclude the presence of genetic causes in PIPO. Weng: None. Mastrangelo: None. Variants were primarily identified in autosomal dominant and X-linked genes. The regulatory network suggest an important role of hsa-miR-122-5p as post transcriptional regulator of downregulated genes. The minigene expression system was used to evaluate the functional effect of SNVs on splicing. Guimarães: None. Pignata: None. Variant screening in NF1 was performed in all exonic regions, either by Sanger or next-generation sequencing (Ion Torrent). Compared with controls, patients with PD showed a significantly higher expression of circulating exosomal miR-150-5p, while exosomal miR-132-3p was significantly lower. Barcia: None. CMA was performed in all patients. Results: 336 out of 706 (47.5%) consulted children (mean age 3.9 years) with multiple congenital anomalies with or without developmental delay were suspected of malformative/dysmorphic syndrome. Macintosh: None. Index cases’ samples were analysed by NGS sequencing panel of the four HHT causative genes and MLPA; the molecular investigation in patients’ relatives was performed by Sanger sequencing. Deficiency of FKBP22 may lead to accumulation of incorrectly folded collagen molecules in the endoplasmic reticulum (ER), causing premature interactions. Roggini: None. The phenotypic outcome of this rare sex chromosome rearrangement may be attributed to combined dosage effects of genes that escape X-inactivation. Grazuleviciene: None. of Biostatistics, Epidemiology and Scientific Computing, Riyadh, Saudi Arabia, 24UCL Institute of Neurology, Dept. None of the variants were detected in the pseudocontrol population databases (gnomAD exomes, gnomAD genomes, 1000G, ESP, Kaviar) and the majority of the pathogenic predictors suggested a pathogenic effect for the nonsense variant. Kocagil: None. Rodríguez: A. Belezhanska: None. Knopp: None. Añón16, Javier Belda17, Jesús Villar2,6, Carlos Flores1,5,6 1Research Unit, Hospital Universitario N.S. de Candelaria, Universidad de La Laguna, Santa Cruz de Tenerife, Spain, 2Research Unit, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain, 3Instituto de Tecnologías Biomédicas (ITB), Universidad de La Laguna, Santa Cruz de Tenerife, Spain, 4Department of Health Sciences, University of Leicester, Leicester, United Kingdom, 5Genomics Division, Instituto Tecnológico y de Energías Renovables (ITER), Santa Cruz de Tenerife, Spain, 6CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain, 7Servicio de Medicina Intensiva, Complejo Asistencial Universitario de Palencia, Palencia, Spain, 8Department of Anesthesiology, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain, 9Department of Medical and Surgical Sciences, University of Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain, 10Intensive Care Unit, Complejo Hospitalario Universitario de León, León, Spain, 11Intensive Care Unit, Hospital Universitario Rio Hortega, Valladolid, Spain, 12Intensive Care Unit, Hospital General de Ciudad Real, Ciudad Real, Spain, 13Intensive Care Unit, Hospital Virgen de la Luz, Cuenca, Spain, 14Department of Anesthesiology, Hospital Universitario N.S. de Candelaria, Santa Cruz de Tenerife, Spain, 15National Institute for Health Research, Leicester Respiratory Biomedical Research Centre, Glenfield Hospital, Leicester, United Kingdom, 16Intensive Care Unit, Hospital Universitario La Paz, Madrid, Spain, 17Department of Anesthesiology and Critical Care, Hospital Clinico Universitario of Valencia, Valencia, Spain. Texidó: None. J.M. Wit: None. We aim to enroll 500 patients and complete the dataset with WGS and metabolomics data to explore the added value of these technologies. López Grondona: None. Study funded by PI20/01569. Bisphosphonates can be used to treat osteoporosis in patients with LPI. Arranz: None. Conclusions: Of significance is the identification of novel/rare variations in genes linked to obesity by GWAS and mouse knock-outs providing mechanistic leads to genetic identification of severe obesity in human. Pavlyukova2, Alexander F. Introduction: The highly polymorphic CYP2D6 gene impacts the metabolism of 25% of the mostly prescribed drugs. The lack of UQCRC1 subunit-containing subassemblies could result from an impaired interaction with mutant UQCRC2Gly222Ala and subsequent degradation of both subunits by mitochondrial proteases. P17.059.B Prediction of the splicing effects of SNVs affecting the first nucleotide G of an exon Atefeh Joudaki, Jun-ichi Takeda, Akio Masuda, Kinji Ohno Neurogenetics, Nagoya University Graduate School of Medicine, Nagoya, Japan. Autopsy findings showed increased wall thickness of interventricular septum (IVS; 18 mm) and left posterior wall (LPW; 20 mm) with patchy myocardial disarray. In our experience, WGS allowed precisely mapping breakpoints in our patients, constituting an unparalleled opportunity to improve our understanding of genes involved in genetically complex disorders. Selection tests revealed genetic variants under natural selection including in TMEM247, EPAS1, ATP6V1E2 etc. Our in-silico study of the variant’s effect on the protein showed that these alterations cause an important truncation of the protein. These variants are located in genes unlikely related to patients diagnosis. One additional INDEL and three additional SNPs were detected. E.H. Seppala: A. Materials and methods: We recruited five sporadic (patients 1-4) and one familial case (patients 5& 6), all of whom presented a spectrum of craniofacial abnormalities. Introduction: Cantú syndrome (CS) is caused by gain-of-function pathogenic disease-causing variants in the genes coding for ABCC9 and KCNJ8, which together form an ATP-sensitive potassium channel. Conclusion: We report on the seventh fetus with Wieacker-Wolff syndrome. Balinova1, Tatyana A. Two of 34 patients have heterozygous variants - one novel variant NM_012193.4:c.1486del which leads to frameshift resulting in the formation of a premature translation termination site, p.(Trp496Glyfs*17), and one previously described pathogenic variant c.205C>T leading to a missense substitution p.(His69Tyr) causing incorrect folding of the FZD4 protein. Also, as in other North Caucasian populations (for example, in Karachai), in Ossetians the most frequent GJB2 variant was c. M.S. Zaki: None. P11.085.C Genetics of neural tube defects: new candidate genes and complex mode of inheritance Marie Faoucher 1,2, Artem Kim1, Marie Beaumont1, Wilfrid Carre1,2, Hubert Journel3, Linda Akloul4, Laurent Pasquier4, Mélanie Fradin4, Chloé Quelin4, Andrea Manunta5, Erwan Watrin2, Marie De Tayrac1,2, Sylvie Odent4,2, Christèle Dubourg1,2, Valérie Dupé2, Véronique David1,2 1Genetics laboratory, CHU Pontchaillou, Rennes, France, 2UMR 6290 CNRS, IGDR, Univ Rennes1, Rennes, France, 3Genetics department, CH Vannes, Vannes, France, 4Genetics department, CHU Pontchaillou, Rennes, France, 5Urology department, CHU Pontchaillou, Rennes, France. PPP1R35 interacts with several established primary microcephaly (MCPH) genes, and multiple PPP1R35 model organism studies hypothesize PPP1R35 as a candidate MCPH gene. The TLR-mediated response has beneficial roles stimulating phagocytosis releasing neurotoxic products. MAGEA11 showed the opposite behaviour. Methods: LEF1 isoforms expression was evaluated by quantitative real-time PCR in 87 newly diagnosed childhood ALL patients and controls. Plăiaşu: None. However, quantitative PCR revealed markedly decreased TBK1 levels in the patient sample, as compared to three healthy controls. We have studied 108 Spanish families with autosomal dominant sensorineural hearing loss (ADSNHL), 45 of which have been genetically diagnosed, thus constituting a diagnostic rate of 41.67%. Results: Of the 94 reported MS risk variants four showed MS risk association in the exome analysis (EVI5 rs11808092 p = 0.0002; TNFRSF1A rs1800693 p = 0.00003; MTHFR rs1801131 p = 0.038; and CD58 rs1414273 p = 0.00007). At the same time, if we will find any pathological changes, same test will be performed for her sister and mother. We detected CNVs in regions not frequently related to oral clefts (1q, 15q13, 16p11) and describe cleft lip in Malan syndrome (19p13.2). Lynch: None. Goméz-García5, Arjen R. The splicing-type specific effects of our top MR findings were further validated using sQTLs from CancersplicingQTL database, with samples from cancer patients. P05.047.A Novel TRAF2 variant and KDR deletion are implicated in the pathogenesis of pulmonary arterial hypertension Natalia Gallego 1, Shaun Pienkos2, David Condon2, Alejandro Cruz3, Nuria Ochoa3, Julián Nevado1, Pedro Arias1, Stuti Agarwal2, Hiral Patel2, Ananya Chakraborty2, Pablo Lapunzina1, Pilar Escribano3, Vinicio de Jesús2, Jair Tenorio1 1Medical and Molecular Genetics Institute (INGEMM), IdiPaz, Hospital Universitario La Paz, Madrid, Spain, 2Division of Pulmonary and Critical Care Medicine and Department of Medicine, Stanford University, Stanford, CA, USA, 3Pulmonary Hypertension Unit, Department of Cardiology, Hospital Universitario Doce de Octubre, Madrid, Spain. Brunner2,4, S. Rinne: None. E.E. Eichler: None. Rare variants were then analyzed prioritizing genes related to mitochondrial or neuronal function. Conclusions: There is controversy about the role of STAP1 in FH3. Bouhlel: None. Tsarev: None. Here we investigate underlying genetic factors for the five symptom dimensions (depression, negative syndrome, positive formal thought disorder, paranoid-hallucinatory syndrome, and increased appetite). Peeters: None. Introduction: The proper characterisation of the clinical significance of germline variants is of high relevance to reduce the amount of variants with uncertain clinical significance (VUS). Molecular diagnosis is of particular benefit and allows to identify clinically-unrecognized hearing loss syndromes, as well as appropriate management and follow-up, including genetic counselling. duymus: None. Westudied the survival of patients using the Kaplan-Meier method. Perioc: None. Verdonschot1 1Maastricht University Medical Center, Maastricht, Netherlands, 2Imperial College London, London, United Kingdom. Navarro Casado: None. Apart from the latter and excluding CNVs on the X chromosome, 12 were inherited from healthy parents, favoring benignity and lessening the burden of uncertainty. P06.059.D Functional analysis of the PCCA and PCCB genes variants, predicted to affect splicingIgor Bychkov, Artur Galushkin, Aleksandra Filatova, Andrey Nekrasov, Marina Kurkina, Galina Baydakova, Alexandra Ilyushkina, Mikhail Skoblov, Ekaterina Zakharova Research centre for medical genetics, Moscow, Russian Federation. Barakat18, Robert Steinfeld19, Christina T. Conclusion: The overall odds of IFs is low. 10% of pathogenic or likely pathogenic variants exhibit geographic heterogeneity. Mombach: None. M.O. Acar: None. Beetz: A. Biallelic mutations in BUB1B, CEP57 and TRIP13 have been identified as the underlying cause of MVA 1 (OMIM 257300), MVA 2 (OMIM 614114) and MVA 3 (OMIM 617598) respectively. Farhat Hached University Hospital, Sousse, Tunisia, 6Department of Dermatology and Venerology. 37% (72/194) had a laboratory-confirmed genetic diagnosis. She was born at 33 weeks of gestation to healthy unrelated parents with no relevant family history. Mounguengue: None. 28%; p = 0.01). 22251; ANR, GENOMIT ANR-15-RAR3-0012-07 G. Masuda: None. P15.014.B Inhibition of MAD2L2 and NUDT16L1 impacts homology directed repair in CRISPR-Cas9 gene editing Arina A. For these reasons, it is difficult to define a specific clinical phenotype in these patients. Tiranti: None. Mosiello: None. Pavlová: None. Carrié: None. There is a need for training of the genetics residents and practitioners in the concepts of algorithmics, NGS data analysis, statistics, and massive data management. Conclusions: The efficiency of correcting a single nucleotide deletion in the EGFP gene increases by synchronization of cell cycle in the G2/M phase in HEK293T culture, apparently due to the activation of HDR. We report an evaluation of prediction accuracy for eye, hair and skin pigmentation based on genomic and phenotypic data for over 6,500 admixed Latin Americans (the CANDELA dataset). Conclusions: Carrier frequencies for these common recessive diseases were obtained for the first time in two cohorts of the Russian population. The patient was born from a faraway consanguineous couple and reported the death of his sister, his maternal aunt and uncle at 45 year-old from digestive cancers. Caspar 1,2, Patricia Stoll1, Janine Meienberg1, Gabor Matyas1,3 1Center for Cardiovascular Genetics and Gene Diagnostics, Foundation for People with Rare Diseases, Schlieren-Zurich, Switzerland, 2Laboratory of Translational Nutrition Biology, ETH, Schwerzenbach, Zurich, Switzerland, 3Zurich Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland. P11.123.A Tenorio syndrome: description of 9 new cases and review of the clinical and molecular features Jair Tenorio 1, Pedro Arias1, Alberto Fernandez-Jaen2, Guillermo Lay-Son3, Allan Bayat4, Laurence Olivier-Faivre5, Natalia Gallego1, Sergio Ramos1, James Lespinase6, Frederic Tran-Mau-Them7, Fernando Santos-Simarro1, Lucile Pinson8, Antonio Federico Martinez-Monseny9, María del Mar O´Callaghan Cord9, Pablo Lapunzina1 1Institute of Medical and Molecular Genetics (INGEMM) - Hospital Universitario La Paz, Madrid, Spain, 2Hospital Universitario Quirón de Madrid, Madrid, Spain, 3Pontificia Universidad Catolica de Chile, Santiago de Chile, Chile, 4Department of Pediatrics, Hvidovre Hospital. A.L.G. Soares: B. Orini: None. These individuals were divided by their health status into case (with OHP) and control groups (without OHP). The patient has waddling gait with mildly anterior pelvic tilt and thoracic scoliosis. Results: In the human lung tissue (E-GEOD-8581), and in the COPD blood (GSE54837) datasets, we identified 691 and 743 DEGs respectively, and 63 shared between them. We calculated composite brain signatures reflecting cortical thickness of specific age or AD vulnerable brain regions. C.M. Moya: None. Triki: None. Gerundino: None. World-wide collaborations have identified association of ~270 common loci, with small individual effect and hence weak clinical implications. In a mouse model overexpressing human-Cyr61 (hCyr61) in the fat tissue, we see an increased body fat percentage under a high fat diet (HFD), due to a switch in body composition (higher fat mass, lower lean mass), while body weight did not differ from WT mice. Zhekaite: None. Anadiotis: None. All detected imbalances by aCGH were submicroscopic (in range 0.19-2.6Mb) and 2 out of 6 (33.33%) were classified as causative for the spontaneous misscariage. The participants attended two sessions in which behavioral experiments, structural and functional magnetic resonance imaging (MRI) data, psychophysiological as well as metabolic parameters and gut microbiota samples were collected.16S Amplicon sequencing was done on the gut microbiota samples on the 16s region. Material and methods: Using CMA, microdeletions at chromosome band 19p13.11 were detected in four independent individuals presenting with a DD/ID phenotype. Conclusions: We highlight the utility of widefield retinal imaging in individuals suspected to have NCMD and provide further evidence supporting the role of PRDM13 dysregulation in the pathogenesis of this condition. Deryabina: None. Functional analysis of newly identified CNVs needs to follow. Tele-consultations were not possible in cases when: a. Pang: None. D.R. Stewart: None. Lill14,17,18, Janine Magg6, Aleš Maver19, Danielle C. Telomeres are located at the ends of chromosomes and consist of tandem repeats TTAGGG. STR analysis was used to determine the parental origins of the tetraploid chromosomes. We also find a large role of metabolic factors that affect not only gestational diabetes, but also the other traits. The software is accessible to users via a modern web browser. Cantarín Extremera: None. 1, Kharkiv, Ukraine. More often hypermethylated status was found among patients with perinatal loss - 57,14%. Puzzono: None. To correct for ascertainment bias, proband phenotypes were omitted. Guinand: None. Introduction: Genetic carrier screening is an advanced tool for reducing recessive disease burden. Gennarelli: None. Whole exome sequencing was performed for the patient followed by targeted sequencing of the TH gene for his family, using an Illumina MiSeq platform. Vissers1,2, Simon E. Our group has previously identified a novel missense variant in TTBK2 (c.625C>T; p.L209F) in two Portuguese siblings with a diagnosis of cerebellar ataxia. To better understand aspects of transition (so far there are no international guidelines available), Rare Disease Centre in Gdansk, Poland, organized workshops for patients and carers (P&C) and medical professionals (MP). Conclusions: Thus, we reached 5-fold enhancement of HDR that can be used in editing of pathogenic human mutations. Efficiency of variant discovery from NGS data depends on multiple factors, including the performance of read alignment and variant calling algorithms. Often this carrier couple status will not be known until the birth of an affected child, yet new technologies facilitating the rapid simultaneous testing of many different carrier states- expanded carrier screening (ECS)- now mean those couples at risk can be identified before they conceive. Shestak: None. Chan Pak Choon: None. Current diagnostic and prognostic genetic testing for leukemias relies largely on cytogenetic methods. A.N. Meshkov: None. P23.011.C What specialists talk about medical genetics in Russia? The pathway consists of a mitochondrial xenobiotic/medium chain fatty acid: CoA ligase (ACSM2B) and glycine N-acyltransferase (GLYAT). Marziliano: None. Waanders: None. The most common type of dementia is Alzheimer’s disease (AD), which affects 65-70% of patients over 65. Abbott: None. P10.042.B The c.794C>T p.(Ala265Val) SCN4A variant may be associated with congenital myopathy with FSHD-like phenotype Barbora Plevová 1, Jana Zídková2, Petra Laššuthová3, Roope Männikkö4, Jana Haberlová1 1Department of Paediatric Neurology, Second Faculty of Medicine (2. An increased risk of MLID has been associated with assisted reproductive technology births and genetic causes may be identified in a small subset of patients (e.g. biallelic ZFP57 mutations). Delea: None. We extracted 59 measurements from landmarks manually placed on photographs (2D) of the right profile of the volunteers and performed genetic analyses with nearly 9M imputed or genotyped SNPs. Results: We found significant association of 32 traits with at least 1 (and up to 6) of 32 different genomic regions. Reimand: None. Kogan, Vladislav S. Felício: None. T.B. Laurberg: None. Behrens: None. Material and Methods: Whole-exome sequencing (WES) of germline samples was performed in 20 early-onset GC patients without previous germline mutation identified. Conclusions: Our approach proved to be efficient in identifying the molecular causes of NSHL, leading to an overall detection rate of ~50% in the Italian population. So far, our study (Almuhaizea et al.) and that of Diaz et al. Cigarette smoking, for example, can directly derange folliculogenesis by ROS production. Sowińska-Seidler: None. S.I. Ferreira: None. T.P. Shkurat: None. Lamouroux: None. Denis-Musquer: None. STR expansion disorders are a family of neuropathological disorders linked to the accumulation of STRs and are currently detected with PCR techniques. Moreover, trisomy 16 is frequently found confined to the placenta, with a chromosomally normal fetus. Pedrolli: None. O.T. Oleksyk: None. The differences were significant (p C (p.Glu2904Gln) was classified as likely pathogenic. We ran GWAS on all traits correcting for age, sex, array used, and genetic ancestry. Congenital mypoathies are rare neuromuscular hereditary disorders that manifest at birth or during infancy and usually appear with muscle weakness and hypotonia. I.N. Mohammed: None. Gisladottir: None. Differences between groups were assessed using Student’s t-test and results were considered to have statistically significant difference if p 4 min). Background: Liquid biopsy is a new technology to analyze circulating tumor DNA (ctDNA) from tumors. B.L. Freire: None. Conclusion: Our study confirms the role of previously described modifier genes and points out new candidates to explore. Sanger sequencing for cosegregation analysis was able in only 6 of 17 VUS with high probability of pathogenicity. Paglia: None. We correlated the diagnostic yield to the major ultrasound findings, which may help to establish high risk ultrasound findings, needing investigation beyond fetal karyotyping or CNV analyses. Ribeiro: None. Gene-level expression data was accessed from the AMP-PD portal and the CoExpNets package was used to generate a co-expression network. Four patients presented additional CNVs on chromosomes 8, 16 and 17. Arenaza-Urquijo1,4,5, Carolina Minguillon1,4,5, Karine Fauria1,5, Immaculata De Vivo6,7, Arcadi Navarro1,8,9, José Luis Molinuevo1,10, Juan D. Morín: None. Jackson: None. To study follicular lymphoma we performed a bone marrow study to rule out the presence of atypical lymphocytes and bone marrow involvement. The deletion includes the first four exons of CREBBP. GA+AA was a negative prognostic factor for DFS (multivariate HR 2.248, p = 0.025) and OS (multivariate HR 2.248, p = 0.029). Funding: Ministerio de Ciencia e Innovación (CGL2017-89021-P), the Basque Government (GV-IT1138-16), Doctoral Fellowship to S.O.L. (PRE_2018_1_0068), and Cabildo Insular de Tenerife (CGIEU0000219140). This includes clinical entities such as hereditary sensory and autonomic neuropathies (HSAN) and congenital insensitivity to pain (CIP). Santen*: None. M.P. Soares: None. In the present study, we investigated by Whole Exome Sequencing (WES) analysis a total of 200 ID/ASD patients. P03.010.B The use of high throughput sequencing for the identification of variants contributing to autosomal dominant polycystic kidney disease in the Maltese population Maria Cini Masini 1, Francesca Borg Carbott1, Ritienne Attard1, Adrian Pleven1, Karen Cassar2, Roberta A. Case A is a woman diagnosed with a colorectal adenocarcinoma at age 46, followed by a colorectal adenoma at 48 and multiple myeloma at 50. The median age of carriers is 43 years old. Cluster 1: syndromic epileptic encephalopathy (HP:0200134), ASD (HP:0000729, HP:0000717), Rett-like phenotype, spastic paraplegia (HP:0100021) or suspected mitochondrial disease (HP:0003287). Materials and Methods: The genome-wide association study involved 1174 patients; gene-wise statistics were estimated with VEGAS; differential expression analysis was performed on whole blood samples from 182 patients. We report de novo missense variants in PHF2 in three individuals causing a novel neurodevelopmental disorder characterized by developmental delay, expressive language delay, autistic behavior, stereotypy and facial dysmorphism. In the literature, almost all these mosaic individuals are asymptomatic. Depending on whether a deletion or a duplication of 17p13.3 occurs, different rare neurodevelopmental disorders arise. Results: The pathway inhibitors presented elevated mRNA levels in 7%-18% of the cases and reduced mRNA levels in 27%-59% of the cases. Results: We showed that SARS-CoV and SARS-CoV-2 production substantially decreased in cells with the CT and TM deletion of the BST2 gene, while LAMP1-overexpressing cells exhibited increased production of both viruses. Kostareva: None. Al-Mass: None. Vasileyva1, Sofya A. Moutton: None. van Ravenswaaij-Arts1 1University of Groningen, University Medical Center Groningen, Department of Genetics, Groningen, Netherlands, 2Chromosome 6 Facebook Group, Utrecht, Netherlands. When both oncogenes (E6 and E7) were silenced, we noted an enrichment of MBD2/3 proteins at CDK6, DLC1, NRIP1 gene loci involved in oestrogen receptor (ER) signalling pathway. Molyte: None. Finally, 25% of symptoms in patient data were matched. Introduction: Noonan syndrome represents one of the most prevalent disorders of multiple congenital anomalies.Objective. Shah: None. In this context, the genetic diagnosis of an autosomal dominant TRIO-related disorder is possible but further segregation analysis with samples from parents is required to confirm the variation as de novo. Conclusion: This study demonstrates that laborious long-range PCRs of PKD1 and PKD2 may be replaced by HTS and stringent data analysis reducing cost and analysis time. Pseudotime trajectories showed for the first timeastrogenesis in adult mice from alpha-tanycytes. We extracted gDNA from whole blood of 34 family members and sequenced the coding region of the SERPING1 gene. Basangiu: None. The British Society of Gastroenterologists (BSG) guideline stratifies patients to risk categories (low/population, low-moderate, high-moderate and high) according to FH and known penetrant mutations. Čuturilo: None. P18.040.B Improving the Polygenic Score (PGS) Catalog: updates to submissions, ancestry representation, and score harmonization Samuel Lambert 1,2,3,4, Laurent Gil1,2,5, Aoife McMahon3, Emily Tinsley3, Shirin Saverimuttu3, Richard Houghton1,2,5, Michael Chapman1,2,5, Laura W. Elucidating the expression patterns of pathway’s inhibitors may aid in the selection of suitable cancer patients who would benefit most from the above mentioned targeted therapies. P12.151.C Germline mutations in TP53 and BRCA1 genes in pediatric patients with osteosarcoma revealed by multigene panel testing Vera V. Little is known about experiences and needs of families of childhood cancer patients regarding WES. Also, nominal cQTLs (p G:p.(Ile1891Met) was observed in six patients with high levels of Lp(a). P12.082.B Analyzing clinical behavior of two germline variant in FH gene in a young female patient with renal cancer hereditary syndrome (HLRCC) Jesica M. Background: Head and neck squamous cell carcinoma (HNSCC) includes epithelial malignancies of the oral cavity, pharynx and larynx. P08.006.D Clinical phenotype associated with ARID2 pathogenic variants: a report of twelve new cases and literature review Clara Houdayer 1, Alban Ziegler1, Céline Bris1, Alice Goldenberg2, Antoine Bonnevalle2, Mélanie Fradin3, Christèle Dubourg3, Marie Vincent4, Benjamin Cogné4, Sandra Whalen5, Boris Keren5, Christel Tauvin6, Arthur Sorlin6, Ange-Line Bruel6, David Geneviève7, Rebecca Procopio8, Karen Gripp8, Jennifer Schleit9, Brice Mendelsohn9, Olivier Patat10, Marine Tessarech1, Agnès Guichet11, Dominique Bonneau11, Bertrand Isidor4, Estelle Colin1 1Department of Biochemistry and Genetics, Angers University Hospital, Angers, France, 2Department of Genetics and Reference Centre for Developmental Disorders, Rouen University Hospital, Rouen, France, 3Department of Genetics, Rennes University Hospital, Rennes, France, 4Department of Genetics, Nantes University Hospital, Nantes, France, 5Department of Genetics, APHP, GH Pitié-Salpêtrière, Paris, France, 6Department of Genetics, Dijon University Hospital, Dijon, France, 7Department of Genetics, Montpellier University Hospital, Montpellier, France, 8Division of Medical Genetics, AIdu Pont Hospital for Children, Wilmington, DE, USA, 9Division of Medical Genetics, University of California, San Francisco, CA, USA, 10Department of Genetics, Toulouse University Hospital, Toulouse, France, 11Department of Genetics, Angers University Hospital, Angers, France. Pál: None. Maina2, Philippe Froguel2, Marika Kaakinen1, Inga Prokopenko1 1University of Surrey, Guilford, United Kingdom, 2University of Lille, Lille, France. Xue: None. The deletion is found in the Human Leukocyte Antigen (HLA) region, which plays a central role in many inflammatory and immunological diseases. Conclusions: Functional variants hidden in the LPA KIV-2 CNV have a profound impact on Lp(a) concentrations and CAD risk. The proband’s father has longstanding HCM, a dilated aortic root and atrial fibrillation. Users were able to rapidly investigate the variants in specific genes without needing bioinformatics support. Post-test counselling is crucial for patients’ understanding of genetic testing results. Le Meur: None. Salido: None. Plassard: None. DNA methylation data will be examined using various age prediction models to calculate EAA. Computational analysis of the five single nucleotide variants that are known to cause NCMD revealed that these non-coding changes lie within two putative enhancer elementspredicted to interact with PRDM13 in the developing human retina. Findlay: None. She was born in a normal delivery but with lower birth-weight (2850 g). However, population stratification poses unique challenges in studies of rare variants. Yerezhepov: None. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Modest; South-Eastern Regional Health Authority. In forensics, reliable prediction of lifestyle from DNA traces can be informative in characterizing an unknown donor of a forensic specimen, and thus useful in guiding an investigation. Loveday: None. Carrière: None. Studies conducted on large populations show a lack of connection between vaccination and serious neurological symptoms, although there are isolated cases that indicate such a relationship. Computational modelling revealed significant clustering of the missense variants in the FHA-domain.Here, we present the first prenatally diagnosed PNKP-related primary microcephaly-/encephaly associated with variants affecting the N-terminal FHA-domain. We demonstrated that T-cells depleted of LINE1-RNAs increase their effector responses. Moderate autophagic dysfunction was noted in affected fibroblasts, congruent with the role of IFT20 in modulating autophagy in primary cilia dependent manner in some cellular contexts. elegans. Several studies have aimed to discover non-invasive tools to indirectly evaluate oocyte quality by focusing on CCs as a mirror of oocyte characteristics. Discussion: We report two patients with novel de novo WAC variants, one of which presenting a complex congenital cardiopathy. The first patient presented with Neurofibromatosis type 1, an autosomic dominant disease caused by variants in NF1 gene. Isolated deletion of chromosome 5q (frequency 72%) or del11q (represent 4% of cases) both have a good prognosis.In the literature, these patients have been treated with 5q- isolated syndrome, therefore the patient was proposed to start treatment with Lenalidomide.The presence of these two distinct diseases is an uncommon situation.Cytogenetics plays a significant role in supporting hemato-oncology allowing an accurate diagnosis and consequently targeted therapy F. In conclusion, the tools for variant prioritization provided largely different diagnostic yields, with Exomiser being the best performing tool. P14.021.B 47,XXY/46,XX/46,XY mosaic Klinefelter Syndrome accompanied by mixed connective tissue disorder: A very rare caseAysel Kalayci Yigin, Mustafa Tarik Alay, Deniz Agirbasli, Mehmet Seven Department of Medical Genetics, Cerrahpasa Medical Faculty, Istanbul University-Cerrahpasa, Istanbul, Turkey. The BCFtools package was used for variant calling and the AMY-tree algorithm was applied to determine the relevant set of Y haplogroup markers. We conducted observational and Mendelian randomization (MR) analyses to evaluate the relationship between serum phosphate and BMD. The most pronounced differences between the patients and controls were uncovered in the analysis of myeloperoxidase gene methylation. Gregul: None. Herein, we present the results of the In2Genome Project whose main goal was to develop a multidisciplinary approach to the WES-based genetic diagnosis by having both medical and laboratorial geneticists working directly together in each case. P12.161.A The novel fusion transcripts in pediatric AML with complex 11q23 rearrangement Lilit Ghukasyan 1, Georgii Krasnov1, Arina Bessonova1, Liudmila Baidun2, Tatiana Nasedkina1 1Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Moscow, Russian Federation, 2Russian Children’s Clinical Hospital, Moscow, Russian Federation. Both modules, together containing 5,755 genes, were significantly enriched for terms relating to immune responses including “myeloid leukocyte activation”, “neutrophil activation” and “adaptive immune response”. Although generally accepted as complex traits, many genes play a pivotal role in both pathogenesis and prognosis of autoimmune polyendocrine syndromes. AlBalwi 1,2,3, Aziza Alkhaldi1, Dina Hommam1, Mohammmed Adam1, Alaa AlMeleih1, Abdulelah Abunadi1, Salman Alsaad1, Yazeed Althobaiti1, Hala Alomair1, Ghady Alfaggy1, Barak Alawad1, Alwaleed Almalki1, Ashwag Alghamdi1, Bader Almuzzani1,3, Nasser Alatwi1 1King Abdulaziz Medical City, Riyadh, Saudi Arabia, 2King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia, 3King Abdullah International, Medical Research Center, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia. Caracausi: None. Conclusion: The overall PGV detection rate was 11.59%, with similar rates of BRCA1/2 (7.28%) PGVs as for other actionable PGVs (7.46%), indicating a benefit for extended panel genetic testing in LBC. our patient. Klonowska: None. Epidemiologically-defined clusters displayed specific mutations, suggesting molecular signatures for strains coming from areas that were isolated during the lockdown. T.S. Barakat: None. An upregulation of SAMD9 expression in non-surviving septic patients (p = 0.003) was observed. Siciliano: B. Beside mtDNA nuclear genes are responsible for the mitochondrial function. Purpose: Phosphatidylinositol Glycan Anchor Biosynthesis, class G (PIGG) is an ethanolamine phosphate transferase catalyzing the modification of the second mannose of glycosylphosphatidylinositol (GPI). Erol: None. Lee: A. Ellwanger: None. P04.082.C Genotype-phenotype correlation of aberrations at 7q21.2-q21.3 locus in patients affected with isolated or syndromic form of split-hand/foot malformation Anna Sowińska-Seidler 1, Magdalena Socha1, Anna Materna-Kiryluk1,2, Aleksander Jamsheer1,2 1Department of Medical Genetics, Poznan University of Medical Sciences, Poznań, Poland, 2Centers for Medical Genetics GENESIS, Poznań, Poland. Together, these data expand the spectrum of genes with a role in linear growth and tall stature phenotypes. Results: According to our data, the alleles HLA-DRB1*04, HLA-DRB1*01, HLA-B27, PTPN22 (rs2476601), TNF (rs1800629), TPMT (rs2842934), IL4 (rs2243250) and genotypes HLA-DRB1*04*04, HLA-DRB1*01*16, PTPN22 (rs2476601), TPMT (rs2842934) were significantly associated with the development of the disease in patients. Morleo: None. filippi: None. Conclusion: We have discovered somatic mosaicism in coronary artery cells affected by atherosclerosis. Thus, an association of the 23525T>A polymorphism of the FTO gene with a disturbance in the rate of puberty in adolescents was revealed. In this case the abducted thumbs have been previously observed in patients and the short long bones may already reflect the short stature often typical only in adulthood, suggesting it can be more common prenatally. Employment (full or part-time); Modest; GeneDx. A. However, the implications of copy number gainof these genes cannot be accurately assessed. Conclusion: We suggest the necessity of a full panel NIPT instead of a narrow panel NIPT for better time management of pregnancy and in mosaic trisomy 7 where UPD is excluded. The database (Progenetix) contains information about both CNVs and SNVs as well as NCIt and ICDO codes for the disease origin. McLaughlin9, Rebecca Truty9, Sonal Mahida10, Julie S. Wicher: None. Main syndromes, key testing and specific genes are included. Picciolini: None. The syndrome is caused by a 1.5 to 3.0-Mb deletion in q11.2 region of chromosome 22. al 2019) and the analytical ecosystem FASTGenomics. Employment (full or part-time); Significant; Genom Ltd. Ye: None. P06.021.B Mutations in MCAT cause a nuclear LHON-like optic neuropathySylvie Gerber1, Christophe Orssaud2, Josseline Kaplan1, Jean-Michel Institut Imagine Rozet 1 1Laboratory of Genetics in Ophthalmology (LGO), INSERM UMR1163, Institute of Genetic Diseases, Imagine and Paris Descartes University, 75015 Paris, France., PARIS, France, 2Unité Ophtalmologie, Hôpital Européen Georges-Pompidou HEGP, 75015 Paris, France & Centre de Référence des Maladies Rares en Ophtalmologie (OPHTARA). HPO terms were assigned according to the most relevant clinical features in the medical record and each patient was categorized based on the number of terms selected: 1; 2 to 5; 6 to 10; more than 10. Her phenotype resembles Angelman syndrome and she has marked microcephaly - OFC 44.5cm (-4 SD). To evaluate the selectivity of CRISPR-Cas13a on guide RNA (gRNA) design, we first knocked down the firefly luciferase mRNA. GSPT2 was suggested as the causal gene for the intellectual disability. Background: Liquid biopsy is an alternative tool for discover tumor-specific mutations. Results: 41 families with 105 family-members were found to carry CTNNA1-germline variants. ArrayCGH was perfomed using a custom array specifically designed to investigate intragenic CNVs in hearing loss related genes. In silico analysis, predict a deleterious effect of this variant. Pollak: None. Only ten SNPs had rank scores >2 for the iHS CEU score. Funding: Estonian Research Council grants PRG471 L. Overall analysis time was reduced from over two hours to GH substitutions are more frequent at earlier stages of tumorigenesis and in cancers derived from slow-replicating tissues. Cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS) has been recently linked to a biallelic expansion of a polymorphic pentanucleotide repeat in intron 2 of the replication factor C subunit 1 (RFC1) gene. Neerincx1, Morris A. In our study we have focused to specific and novel VHL mutations mostly related to retinal and cerebellar haemangioblastomas manifestation in Slovenian population. As such, we identified a decrease in mobility, longevity, and synaptic efficacy in mutant worms compared to the wt. However, more extensive data from other studies suggest the opposite trend. Milanovski: None. For tumor testing, DNA was extracted from FFPE and in-house MSI multiplex PCR method (adopted by Pagin A et al., 2013) and/or SALSA MS-MLPA ME011 (including BRAF V600E mutation) was performed. Villaverde: None. I.N. Lebedev: None. The research is conducted under the state target program: project FSRG-2020-0014 “Genomic of Arctic: epidemiology, hereditary and pathology” M. Twenty-seven individuals had truncating or splice variants, and 10 had missense variants. Results: The allele (p = 0.002) and genotype (p = 0.006) frequencies differed only in the rs533984 of the MRE11A gene belonging to the DNA repair pathway, with the longevity allele G being more frequent in the old cohort. P14.010.C From cytogenetics to cytogenomics - what is the underlying idea? K.A. Patel: None. On the other hand, in 6 out of the 10 patients only studied by WES, the causative changes were identified. Dubied: None. Our results suggest that ULs with an apparently normal karyotype revealed in vitro consist of both karyotypically normal and heteroploid cells. We investigated the wider population health risks and benefits of prolonged sex hormone exposure from such interventions. Several other family members on the mother’s side have short stature and variable cardiac abnormalities. TRS-causative variants can be clinically actionable and lead to intensive surveillance and/or risk reducing surgery that improve morbidity and mortality. The corresponding frequency in deceased individuals with cardiomyopathies was 35%. However, the clinical features of the younger sister consist of bilateral anophthalmia, congenital heart defect (CHD), right split foot with 4 toes and 5 metatarsal, second toe polydactyly, right hand preaxial polydactyly and mild bilateral deafness. Pagnamenta25, Jennifer E. Furthermore, we demonstrated a more relaxed chromatin state in lymphoblastoid cells harboring the p.(Asp551Gly) variant compared to control cells, conferring susceptibility to DNA damage. Hückert4, Jens Kunze4, Claudio Lottaz1, Christoph A. Predisposing genetic factors are suspected, although current genetic knowledge of these pathologies is scarce. Introduction: Results from prenatal Chromosomal-microarray-analysis (CMA) include variants with uncertain clinical significance (VUS), low-penetrance susceptibility-loci (SL) and risks for late-onset conditions. Pieters3,4, Wendy Rodenburg2, Robert-Jan H. Three different pathogenic mutations in EFTUD2 gene were found, in cases 1 and 2 through targeted gene sequence and in case 3 through exome sequence. Many of the important roles of microtubule- and actin-associated proteins in regulating the dynamics of the cytoskeleton during neuronal migration have been uncovered through the study of genetic variations that lead to lissencephaly in human and neuronal migration defects in mouse. N.W. Saadi: None. Specialized computer programs/dysmorphology databases were applied. This rare finding’s contribution to the literature is notable. S.K. McDonnell: None. Conclusions: Young adults with NET present a high rate of P/LP variants in CPG, including several DNA repair genes. Trujillo-Tiebas: None. Such IC50s were markedly reduced upon combination at 0.8, 2.2 and 5 μg/ml on huh7, HCT116 and Vero, respectively. Besides, more than 50% of sequence variants were reclassified from their previous categorization in ClinVar after careful manual analysis. Sorrentino: None. Panel testing included both sequence and copy number variant (CNV) analyses of NGS data from a clinically validated exome assay . J.M. Cameselle-Teijeiro: None. Ohkawara: None. Results are currently being analysed. P.A. Sanchez-Lara: None. Analysis of the FSHD1 locus was followed by next-generation sequencing (NGS) using a custom-designed neuromuscular gene panel. Results: Pathogenic variants were identified in 198 (15,3%) cases, likely pathogenic in 386 (29,7%) and variants of uncertain clinical significance in 548 (46,0%). The duplication lies within a single regulatory chromosomal topographical active domain. Moreover, functional, gene ontology and network analyses were performed. Two families with CELSR1 mutations causing a premature stop codon were tested on mRNA level without detecting nonsense mediated mRNA decay. González Gutiérrez-Solana: None. A well-known risk factor for having a child with T21 is the increased age of the mother. Conclusions: These analyses highlight the sarcomeric assembly, cardiac development and vasculogenesis as key contributors to the spQRSTa. The findings provide insight into possible mechanisms underlying the association with risk of arrhythmogenesis and SCD. Charpentier and J. Vaisitti: None. Results: After the phenotypic classification, the most common SRD were

ciliopathies (36%). it has never been described before that the compound heterozygosity of these mutations causes photosensitive TTD. The study of variants in MTHFR and LPA could help to better predict the cardiovascular events since homocystinuria and Lp(a) plasma levels have been considered as cardiovascular risk factors. Due to its rarity, nonspecific or atypical clinical appearance, some of the successfully revealed AR ataxias were solved by using exome sequencing. Newborn screening (NBS) uses tandem mass-spectroscopy (MSMS) to measure the amino acid levels. Interactome-based approaches to complex diseases have proven successful to fill the gap of knowledge between gene-level findings and pathological phenotypes. Conclusions: The missense variant c.2819C>G (p.Thr940Ser) in exon 21 of NF1 gene has a very low population frequency (1.655x10-5) in ExAC database. Palau: None. Our next step will be investigating somatic mosaicism using different tissue samples from proband. R.M. Smits: None. O.A. Vedyasova: None. Hengeveld 1, Alice Vajda2, Mark Heverin2, Orla Hardiman2, Russell L. One patient has a hemizygous mutation on X linked inherited PHKA1 gene. Conclusions: In this study, we found two novel heterozygous variants associated with the extremely rare diseases Lissencephaly 9 with complex brainstem malformation (LIS9 [MIM no: 618325) and Van Esch-O'Driscoll syndrome (VEODS [MIM no: 301030]). GWAS have been performed for an increasingly wide array of human traits. Collot: None. Fogolari: None. Pineda: None. Disease-free survival and overall survival was decreased in patients with combined variants compared with other patients (44.4% vs 87.3%; 66.7 % vs 96.4%, p T and FAT4:c.3055 C>A heterozygous mutation was detected. CNVs are inferred with Hidden Markov probabilistic Models at the nucleotide-level in the Wavelet compressed space, while existing methods utilize fixed length windows or exon averages. NGS analysis allowed identification of new heterozygotic variant p.Glu367GlyfsTer17 (c.1095_1096delAA) in the ASXL3 gene. Introduction: Cystic fibrosis (CF) is a common, life-limiting monogenic disease, which typically manifests as progressive bronchiectasis, exocrine pancreatic dysfunction, and recurrent pulmonary infections. A.S.L. Ovesen: None. Glavač: None. Leon: None. Ownership Interest (stock, stock options, patent or other intellectual property); Significant; BioMarin Pharmaceutical Inc. goksel tulgar: None. Introduction: Neurodevelopmental disorders(NDDs) are genetically and phenotypically highly heterogeneous. Myasoedov1, Svetlana A. Hofstra1, Monique E. As teenagers and young adults they exhibit elevated ferritin levels, as high as 1600 ug/L. Denizeau: None. Conclusions: The phenotype of TBRS included intellectual disability and overgrowth, with frequent clinical associations included joint hypermobility, obesity, hypotonia, behavioural/psychiatric issues, kyphoscoliosis and afebrile seizures. Germ cell loss did occur during meiosis but not due to incomplete synapsis of the chromosomes. Pavel: None. Martin Merida: None. P03.046.B Application of NGS sequencing for improved diagnosis in the pediatric nephrology setting Radosveta Bozhilova 1, Olga Beltcheva1, Galia Zlatanova2, Kunka Kamenarova1, Kalina Mihova1, Felitsiya Shakova1, Dimitar Roussinov2, Maria Gaydarova2, Vanio Mitev1, Radka Kaneva1 1Molecular Medicine Center, Dpt. Jerez-Calero: None. van Diemen, Kristin M. The other two de novo variants affect highly conserved amino acids in the plant homeodomain PHD, c.23G>C; p.(Cys8Ser) and c.125C>T; p.(Ala42Val). Individuals are experiencing systems- and policy-level challenges yet employing individual-level coping strategies. Results: We characterized the breakpoint position in Xp22.13, with a 15pb deletion, disrupting the intron 1 of NHS. The phenotypic severity of the disease may be influenced by several modifying factors: SMN2 gene and other genes like: BIRC1, NAIP, RAD17, GTF2H2, SERF1A, N-Cadherin-like. In the effort to overcome this limitation, we have applied a new 10x linked-read sequencing technology that combines single-molecule barcode with short-read, to solve NGS-negative patients. Affymetrix Cytoscan 750 CMA revealed a 128 Kb interstitial deletion at 16p13.3, in a male fetus: arr[GRCh37] 16p13.3(3840720_3969211)x1. Lykoskoufis 1, Halit Ongen1, Evarist Planet2, Didier Trono2, Emmanouil T. Conclusions: A novel variant and three previously reported variants were identified in seven Middle Eastern families, further delineating the molecular basis and genotype-phenotype correlation of citrullinemia type 1. While five patients have the Saudi founder p.Asn291Asp variant, one subject has a novel deletion. CES was performed to screen among the neuromuscular genes, the disease-causing mutation more precisely. Introduction: Miller-Dieker syndrome is caused by a contiguous gene deletion syndrome involving multiple genes on chromosome 17p13.3, especially PAFAH1B1 and YWHAE. Materials and Methods: A retrospective study was carried out on 744 IRD affected individuals (from 266 unrelated families) using different molecular techniques, including gene panel, whole exome sequencing, and MLPA hybridation arrays. Also, the statistical analysis showed that G allele confers protection from this disease. The ratio between coverages of mutant and wildtype alleles, compared to those obtained with known dilutions of the mutant allele, provided an estimate of the mosaicism extension (12.18%) (A). Five open questions explore the families' perception of manifestations which most affect health and quality of life of their relative, events of adverse reactions to treatments, etc. Papakonstantinou: None. Bonotto: None. Srebniak 1, Fernanda S. Although 38 SCA genes are known, approximately 25% of patients remain genetically undiagnosed upon testing of the coding regions of SCA genes for variations. P11.094.D Lymphatic problems in patients with Noonan SyndromeJos Draaisma1, Jessie Swarts 2, Lotte Kleimeier1, Erika Leenders3, Willemijn Klein1 1Rradboudumc Amalia children's hospital, Nijmegen, Netherlands, 2Radboudumc Amalia children's hospital, Nijmegen, Netherlands, 3Rradboudumc, Nijmegen, Netherlands. P02.050.C A newborn with corneal clouding and a diagnosis of posterior polymorphous corneal dystrophy type 1 due to a duplication of the OVOL2 gene Hester Y. The IL8 gene expression was characterized by the most pronounced increase (9.83 times versus control), while the IL1RL1 gene demonstrated the most pronounced decrease in its expression (4.17 times). Premature births, polyhydramnios and large for gestational age newborns are perinatal factors also seen in the family. Material and methods: study-cohort included 41 OAVS-affected subjects and the tissue-matched methylation profiles of 48 anonymous healthy individuals. de la Durantaye: None. Our analysis revealed correlations among inhibitors' relative mRNA levels with clinicopathological characteristics and multiple patterns of simultaneous expression. Behavioural traits have distinct genetic correlations with brain morphology that suggest trait-specific relevance of ROIs. R. It was considered accessible for people with varying levels of education, although some had difficulties understanding the key concept used in genetic counselling, such as, 'genes' and 'inheritance'. Materials and methods: As part of the EPIC-Vision study, we collected patient (age≥18) reported AQoL-8D data as part of a customised survey. Awayda: None. Revealing the clonal architecture and a mutational profile of leukemic cells may contribute to optimal therapy tailoring. Elgaeva 1, Maxim B. Carreño Salas: None. He was the second-born from a consanguineous marriage at 33+5 week gestational age. J.M. Soria: None. It is known to be responsible for different bone pathologies according to its alteration mechanism: brachydactyly in case of mono-allelic loss of function; symphalangism and multiple synostoses in case of heterozygous gain of function; Grebe, Du Pan and Hunter-Thompson syndromes in case of bi-allelic loss of function; susceptibility to osteoarthritis and hip dysplasia in the presence of polymorphisms within its promoter. 5 affected individuals (11.1%) showed α/α polymorphism of SAA1 gene. 8%), switched from imatinib to nilotinib (24% vs. Laššuthová: None. Cackowski: None. Boschann: None. The scientific data to guide management of PJS are sparse. The detected variants were investigated in HGMD (Human Genome Mutation Database) and EAHAD-CFDB (EAHAD Coagulation Factor Variant Databases). Gambin: None. P17.048.C Multi-omics to predict changes during cold pressor testLisette J. Wouters1, Janna A. This work was supported by the Russian Foundation for Basic Research (project No.18-29-09020). L.S. Fouda: None. The samples with scores higher than fourteen were classified as microsatellite unstable with high confidence (MSI-HC). A.R. Mensenkamp: None. Perez de Castro: None. Our case clearly demonstrates the importance of performing prenatal array analysis also in cases of isolated bilateral ventriculomegaly. Additionally, the automated method maintained the wide dynamic range of the GoTaq kit. S.N. van der Crabben: None. Introduction: Autoimmune thyroiditis is a chronic inflammatory process characterized by the presence of glandular lymphocytic infiltration and thyroid specific antibodies. Galbete: None. Future work will integrate other AWMGS NGS assays into the software. Ambrosetti: None. Ehsan: None. Genetic counselling is a fast-growing profession in Canada, but despite this growth, is only recognized legally in 1 of 13 Canadian provinces and territories. Results: Among 1285 Russian patients secondary findings have been identified in 36 cases (3%). One of the approaches to increasing HDR is the use of various agents that synchronize cells in the G2/M phase. Oz: None. Lois: None. We investigated of associations with clinical criteria (DAS28-CRP, HAQ-DI, CDAI) and biochemical factors (ACPA formation, RF, CRP). P.A. Nagtegaal: None. Thorburn: None. The Birt-Hogg-Dube' (BHD) syndrome is an autosomal dominant inherited disorder due to loss of function germline mutations in the folliculin (FLCN) gene. The variant segregated with the disease in all available family members. McGorrian: None. Conclusions: TSO500 confirmed its efficacy for the identification of somatic, germline variants, TMB and MSI determination in tumorigenic samples and can be relevant for an improved patient's management and stratification for target therapies. Introduction: HHAT (Hedgehog acyl-transferase) mediates the post-translational modification of downstream proteins in the hedgehog (Hh) signalling pathway. These data reveal that the combination of variants results in a blended phenotype with each gene affecting a different part of the nervous system and nervous system-muscle connection.Interpretation: In patients with MPV and complex blended phenotypes resulting from multiple molecular diagnoses, HPO analysis allows for dissection of phenotypic contribution of both established disease genes and novel gene candidates not yet proven to cause human disease with marked implications for prognosis, treatment, and family counseling for the most complex genetic patients. A large study was conducted to assess the role of SNP rs7969300 as a modifier of the age of onset in SCA2 patients. Öiglane-Šlik: None. Heimler syndrome is one of the PBDs that is caused by mutations in PEX1 and PEX6 genes. Vajro: None. Kero: None. Introduction: Antimicrobial-resistant bacteria are contributing to mortality and morbidity worldwide. Materials and Methods: Between October 2018 and December 2020 400 consecutive children with newly diagnosed BCP-ALL and treated according to AIEOP-BFM ALL 2017 Poland protocol were enrolled into this study. Pignolet: None. Symoens: None. All cases showed several additional abnormalities of unknown clinical significance by OGM. Venckute: None. Results: Clinical and cytogenetic analyses of the two PT21 children reported here revealed specular features: one case with the HR-DSCR among the duplicated regions is diagnosed with DS, while the other without the HR-DSCR duplication has no DS diagnosis. P02.069.B Clinical and molecular revaluation yield a 52% of characterization in syndromic retinal diseases Irene Perea-Romero 1,2, Fiona Blanco-Kelly1,2, Iker Sanchez-Navarro1, Isabel Lorda-Sanchez1,2, Saoud Tahsin-Swafiri1,2, Almudena Avila-Fernandez1,2, Inmaculada Martin-Merida1,2, Maria Jose Trujillo-Tiebas1,2, Rosario Lopez-Rodriguez1,2, Ionut Florin Iancu1,2, Raquel Romero1,2, Mathieu Quinodoz3,4,5, Pablo Minguez1,2, Marta Corton1,2, Carlo Rivolta3,4,5, Carmen Ayuso1,2 1Health Research Institute-Fundación Jiménez Díaz University Hospital, Universidad Autónoma de Madrid (IIS-FJD, UAM), Madrid, Spain, 2Center for Biomedical Network Research on Rare Diseases (CIBERER), Instituto de Salud Carlos III, Madrid, Spain, 3Institute of Molecular and Clinical Ophthalmology Basel (IOB), Basel, Switzerland, 4Department of Ophthalmology, University of Basel, Basel, Switzerland, 5Department of Genetics and Genome Biology, University of Leicester, Leicester, United Kingdom. He was the first child of non-consanguineous Turkish parents. Bergamini: None. Zsigmond: None. P08.023.A Molecular analysis of a novel donor splice site variant in DYNC1H1 Gunda Petraitytė, Živilė Maldžienė, Violeta Mikštienė, Evelina Siavrienė, Tautvydas Rančelis, Vaidutis Kučinskas, Eglė Preikšaitienė Department of Human and Medical Genetics, Institute of Biomedical Sciences, Faculty of Medicine, Vilnius University, Vilnius, Lithuania. Williams1 1King's College London, London, United Kingdom, 2Novosibirsk State University, Novosibirsk, Russian Federation, 3PolyOmica, 's-Hertogenbosch, Netherlands, 4University of Washington, Seattle, WA, USA. Analysis of the simultaneous gene expression revealed linear correlations among different inhibitor pairs, with the strongest ones between MCL1/cFLIP (R = 0,741, p in exon 5 of the PTEN gene in heterozygous state in patient B, it was inherited from his affected mother, c.59delG in exon 1 of the PTEN gene in heterozygous state in patient C, the variant arose de novo. Pathogenic variants are associated with autosomal dominant congenital heart defects (OMIM #614980). Here we describe a 5-month-old boy with delayed psychomotor development and mild phenotypic features (such as bitemporal narrowing, slightly protruding ears with up-lifted lobes, posterior plagiocephaly). Mutations in SORD have been recently identified as a frequent and potentially treatable cause of autosomal recessive CMT, presenting as axonal or predominantly distal motor neuropathy. Most DDL also have gene amplification MDM2 and CDK4, which may be similar to other tumors (Intimal sarcoma, Parosteal osteosarcoma, low grade central osteosarcoma, etc.) Conclusion: For the diagnosis and correct classification of the DDL, it is essential to carry out a cytogenetic study, Immunostaining for MDM2 and CDK4 or molecular testing for 12q13-15 amplification. The activity of alpha mannosidase, the identification of pathogenic variants in MAN2B1 by next-generation sequencing, and the mannose-rich oligosaccharides urinary level were determined by external laboratories. Hereditary thrombophilia increases the risk of pregnancy associated VTE up to 34-fold. Heterozygous carriers of WDR11 loss-of-function variants in our families were healthy and did in particular not show any obvious clinical signs of hypogonadotropic hypogonadism as seen in patients with heterozygous missense variants. Fulya Yaylacioglu Tuncay 1, Beril Talim2, Pervin Rukiye Dinçer3 1Department of Medical Biology, Gulhane Medical Faculty, University of Health Sciences, Ankara, Turkey, 2Department of Pediatrics, Faculty of Medicine, Hacettepe University, Ankara, Turkey, 3Department of Medical Biology,Faculty of Medicine, Hacettepe University, Ankara, Turkey. Fundings. ILIAD consists of 2 components: a central, web-based registry and a network of linked satellite/client registries forming the ERN-ITHACA registry federation. Peshehodko: None. Materials and Methods: Rare variants were selected from patient exome sequencing data to perform a gene burden analysis. P17.083.B Variant Interpretation Pipeline: a modular pipeline that integrates best practice methods to prioritize genetic variants causal for a patient's phenotype Lennart F. J.H. Tobias: None. Semerci Gündüz1,2 1ANKARA YILDIRIM BEYAZIT UNIVERSITY, Ankara, Turkey, 2Ankara City Hospital, Medical Genetics Department, Ankara, Turkey. Pelleri: None. De Waele: None. Male karyotype with mosaic chromosome 7 trisomy 7p22. In 2020 we have incorporated a high-resolution exon targeted aCGH of 180k (Oxford Gene Technology, OGT). Conclusion: There is strong correlation between the general type of CFTR mutation and clinical phenotype. Hypohidrotic ectodermal dysplasia (HED) is the most common ED form characterized by hypodontia, hypohidrosis, hypotrichosis and in several instances dysmorphic features. The proband came to our attention because her 51 years old daughter required pre-symptomatic genetic counselling. Spanou-Aristidou: None. Methods: Online survey information was collected from 1,614 individuals with rare, common, or no known health conditions over two months, ending November 2020. We expect to facilitate diagnoses for unsolved patients, and to elucidate the molecular underpinning of ITHACA-related unexplained syndromes. The variant was confirmed by Sanger sequencing. Miro Canvas libraries present superior sequencing metrics than manually prepped libraries when PCR-free assay receives very low gDNA input amounts. Two patients had macrocephaly, one of them - delayed closure of fontanel and one patient - abnormal skull shape. The conditional false discovery rate (cFDR) framework provides a tool to leverage one GWAS study to improve power in another. The patient was diagnosed as metastatic lung cancer by using PET imaging in November 2020. Möricke: None. Two patients presented isolated dystonia, while five had more complex or atypical phenotypes. It is caused by mutations in the NHS gene on chromosome Xp22.13. We applied HDL-X on 30 complex traits measured in about 155,000 unrelated British men and 180,000 unrelated British women from the UK Biobank (UKBB). Vialard: None. Almost 33 (26.1%) lifelong premature ejaculatory patients had AR variant of longer (≥26) CAG repeats was homozygous for S alleles (SS), 45 (35.7%) was homozygous for L allele (LL), and 48 (38%) had the L/S or S/L genotype of 5-HTTLPR gene. Branicki: None. TRAF2 encode for immunomodulatory protein that regulate NF-κB activation. Conclusion: Despite low level mosaicism we suggested that ringchromosome r(1) is cause of the phenotype of our patient. Interestingly, the patient also had a Chiari Malformation type I and a subclinical optic neuropathy, which could not be explained by variations in other genes. Introduction: Testing of translocation between chromosome 9 (Abelson murine V gene leukemia viral oncogene homolog1-ABL1) and 22 (Breakpoint Cluster Region-BCR) and mutations in the ABL kinase domain are useful for diagnostic of chronic myeloid leukemia (CML) and guide the treatment. Hereditary multiple exostosis (HME) (OMIM 133700, OIMM 133701) is a genetically heterogeneous disease with an autosomal dominant mode of inheritance, characterized by the presence of multiple cartilaginous growths in the metaphyses of long bones. Facultad de Medicina. We performed rescue experiments by co-injection of MO together with human PLXNA1 mRNA. Malan: None. DMRs were preferentially located in T-cell-specific regulatory regions, showing significant correlations with the expression of 548 DEGs. QTLs for expression and methylation were detected in 771 DEGs and 83 DMR-methylation-correlated DEGs, respectively. The association to COMT, one of the most studied genes in chronic pain field, was not confirmed in the replication analysis. Conclusions: We observe altered mRNA but no protein FKBP5 expression level alterations. Grangeia: None. Z.H. Coban Akdemir: None. She has a significant global developmental delay, microcephaly, mild hypertelorism, broad nasal bridge, nystagmus, partial corpus callosum dysgenesis, hypothyroidism, and bilateral inguinal hernias. Supported by MH CZ - DRO, Motol University Hospital, Prague, Czech Republic 00064203. Cárdenas: None. Engelke1, Eduard Struys2, Lisenka E. This is remarkable as TFEB factor has been reported to be sequestered inside Lewy Bodies, pointing to a role of TFEB in the pathogenesis of PD. We aimed to further elucidate the genetic basis of HSCR in Indonesia. All identified variants were confirmed by Sanger sequencing and validated by parental testing Conclusion: This is the first report of congenital idiopathic arterial calcification caused by homozygous missense pathogenic variant in ABCC6 gene and in combination with Gaucher syndrome. Wong1, So Lun Lee2,3, Martin Knapp4, Brian H. P24.004.C Genome-wide association study of sex effect on asthma susceptibility in African-admixed populations Antonio Espuela-Ortiz 1, Esther Herrera-Luis1, Fabian Lorenzo-Diaz1,2, Michael A. Mussa: None. P19.055.C Genetic markers associated with Alzheimer's disease and schizophrenia demonstrate deviation from selective neutrality in populations of North Eurasia Anna Bocharova, Vadim Stepanov Research Institute of Medical Genetics, Tomsk National Research Medical Center, Tomsk, Russian Federation. Kaplanova: None. Using a large normal prostate tissue eQTL dataset (N = 471) with RNA-Seq and genotyping data, we tested the Kendall's tau rank correlation between normalized gene expression and the PRCA PRS across the full transcriptome. Ranasinghe: None. Ferri: None. However, such family criteria to be used by laymen are non-existent. K.A. de Lange: None. DNA samples were collected from 500 healthy women and 1500 patients with HBOC without detected pathogenic variants in risk genes. P23.045.A Responsible research and innovation in genetics: the challenge of preventive clinical genetics Boy Vijlbrief, Diewertje Houtman, Sam Riedijk Erasmus University Medical Center, Rotterdam, Netherlands. P09.009.D Functional analysis of mutations in a glycosylation enzyme gene, GFPT1, underlying limb-girdle congenital myasthenic syndromes (CMS) Paniz Farshadyeganeh 1, Bisei Ohkawara1, Masayoshi Kamon2, Toshiyuki Araki2, Hirofumi Komaki2, Kinji Ohno1 1Department of Neurogenetics, School of Medicine, Nagoya University, Nagoya, Japan, 2National Institute of Neuroscience (NCNP), Tokyo, Japan. Long-read sequencing coupled with an optimized, robust enrichment method has the potential to illuminate these dark regions. Methods: We prospectively enrolled 713 participants from the UIC AF Registry and UIC Cohort of Patients, Family and Friends. Results: ddPCR testing was concordant with fetal genotype determined following invasive testing in 20 cases. Basal: None. N. M.J.H. Coenen: None. Estevinho: None. Despite reliable coverage, identification of CNVs remains challenging. Giraud: None. This study aimed to characterize mitochondrial bioenergetics and CL content in fibroblasts from TFP/LCHAD deficiency patients. The patient also did not have the right testicle in the scrotum. The analytical evaluation of calcium and phosphate metabolism was normal, excluding rickets. P09.127.D Familywise whole-genome linkage analysis of specific language impairment (SLI) identifies novel loci and replicates previous findings Erin M. One case was suspicious for clonal hematopoiesis in ATM. Woodward1 1Manchester Centre for Genomic Medicine, Manchester Universities NHS Foundation Trust, Manchester, United Kingdom, 2Department of Otolaryngology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom, 3West Midlands Regional Genetics Service, Birmingham Women's NHS Foundation Trust, Birmingham, United Kingdom, 4Yorkshire Regional Genetics Service, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, 5Wessex Clinical Genetics Service, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom, 6Northern Ireland Regional Genetics Service, Belfast Health and Social Care Trust, Belfast, United Kingdom, 7Peninsula Clinical Genetics Service, Royal Devon and Exeter Foundation Trust, Exeter, United Kingdom, 8East Anglia Regional Genetics Service, Cambridge University Hospitals, Cambridge, United Kingdom. Klaa: None. Agrawal5, Allan Bayat6, Thomas M. Farshadyeganeh: None. Liblau: B. Göhring: None. Conclusion: This study revealed novel role for few genes and shed new light on the molecular mechanisms of COPD and lung cancer pathogenesis, and provide potential novel drug targets for both diseases. Conclusions: NOTCH3 (Notch Receptor 3) encodes a transmembrane protein involved in signaling pathways expressed during embryonic development. Deodato: None. We thus begin to unravel the complex genetic regulation of the PTM of two common plasma proteins. The aim of this work was to evaluate the efficacy of read depth-based CNV detection in routine diagnostics. Immunofluorescence staining in control and patient-derived fibroblasts revealed also a marked nuclear localization of Spartin in the mutant cells, whereas in controls it was evenly distributed in the cells. aCGH analysis showed pathological deletion of 5,025 kb segment on 15q26.2 (14 OMIM genes) and additional duplication of 4,179 kb segment on the 1p36.33 chromosome (57 OMIM genes) according to ClinVar and OMIM database. NAV2 is a retinoic-acid responsive novel gene candidate with biological roles in neurite outgrowth and cerebellar dysgenesis in mouse models. Dyer: None. van Diemen University Medical Center Groningen, Groningen, Netherlands. The father of the patient who had similar phenotypic features, also had the same mutation. SYBR-Green-based Real-time PCR assay was used to determine the expression profile of 84 miRNAs (Human miFinder miRNA PCR Array,Qiagen). In particular, miR-26a, major regulator of TGF-β signaling, was found downregulated in both type of exosomes when compared with healthy controls and to hypertension normoalbuminurics (P T;p./Gln200*) heterocygosis. r. The data was analysed using Chromosome Analysis Suite (ChAS) Software (v4.0). P01.098.B Impaired WNT/beta-catenin signaling pathway in the etiology of azoospermia Dunya Aydos 1, Sena Aydos2, Yunus Yukselten3, Asuman Sunguroglu2, Kaan Aydos4 1Ankara University Stem Cell Institute, Ankara, Turkey, 2Department of Medical Biology, Ankara University Faculty of Medicine, Ankara, Turkey, 3Research Laboratories for Health Science, Y Gen Biotechnology Company Ltd., Ankara, Turkey, 4Department of Urology, Ankara University Faculty of Medicine, Ankara, Turkey. The web server is Nginx. Introduction: BRCA 1/2 genes identified as hereditary determinants of a high risk breast cancer (BC). K.B. Gutzkow: None. mRNA-seq analysis permitted to validate the deleterious outcome of two complex rearrangements detected by GS and also find one structural variant and one deep intronic SNV not previously identified by GS alone. Within a month, his neurological status deteriorated leading to a severe intractable epileptic encephalopathy. Valence: None. Iñigo-Campos: None. Objective: To evaluate the risk of fetal involvement when trisomy 8 mosaicism (T8M) is detected in chorionic villus samples (CVS). Meloni: None. Several painful swellings were present due to the multiple bone fissures. Metzler: None. exons 44, 46, 50, 52 and 54). The 5' and 3' untranslated regions (UTRs) and promoter of these genes is poorly studied. Siewert: None. Total RNA was extracted from CCs of all subjects and subsequently reverse transcribed. Contributions of up to EUR 10 000.- (Ten thousand Euros, or equivalent value in kind) per year per company are considered "Modest". Kucharík: A. Introduction: High postprandial lipemia is associated with an increased risk of cardiovascular disease, independent of fasting lipid levels. Thus, in a diploid androgenetic homozygous hydatidiform mole there should be one pair of centrioles, in a heterozygous hydatidiform mole there should be two. L.E. Rawlins: None. Results: Analysis of DNA samples revealed heterozygous donor splice site variant NC_000014.9(NM_001376.5):c.6405+1G>C in DYNC1H1 gene as de novo in the proband's DNA. Llano Rivas: None. Buschmann: None. Montopoli: None. Lenarduzzi: None. This work was supported by EU project 2014-2020.4.01.15-0012, by Estonian Research Council (PUT PRG555 to NT) and by SP1GI18534 grant from Sanofi Aventis Ltd. Total RNA was extracted and reversely transcribed. A.A. Smirnova: None. Leiber: None. P12.099.C Hereditary Cancer Predisposition Testing in Luxembourg Karin Segers 1,2, Marizela Kulisic1, Ben Flies1, Christian Müller1, Philippe Theis1, Karin Dahan1, Barbara Klink1, Daniel Stieber1 1National Center of Genetics (NCG), Laboratoire National de Santé (LNS), Dudelange, Luxembourg, 2Human Genetics Department CHU Sart Tilman, Liège, Belgium. (2016) indicated that the ADPKD point prevalence in the EU is 0.01), Associated with these genes molecular functions and pathways were determined using the online platforms Toppgene and Reactome. Pluta: None. Despite this, African populations are often underrepresented in immunogenetic studies. Whole exome sequencing revealed that each individual carried one of four homozygous missense variants in VPS41. Daviglus: None. The aim of the present study is to describe a Mexican 9-old-months male with 3pdel/13qdup and a novel clinical finding. Karolak3,1, Malgorzata Mrugacz4, Uppala Radhakrishna2, Marzena Gajecka1,3 1Institute of Human Genetics, Polish Academy of Sciences, Poznan, Poland, 2Department of Obstetrics and Gynecology, Oakland University William Beaumont School of Medicine, Royal Oak, MI, USA, 3Chair and Department of Genetics and Pharmaceutical Microbiology, Poznan University of Medical Sciences, Poznan, Poland, 4Department of Ophthalmology and Eye Rehabilitation, Medical University of Bialystok, Bialystok, Poland. Local inbreeding varied from 0.000024 to 0.000587 with average 0.000242. AS is caused by the loss of expression of the maternal copy of the UBE3A gene in 15q11.2-q13 imprinted region. Twelve diagnostic CNVs were reported, ranging in size from 241 bp to 6.7 Mb, representing 5.3% of diagnostic findings. While the rate of such retrotransposition is estimated to be around 1/6200 meiosis, this is only the second observation of a monogenic disease caused by a processed pseudogene insertion. Georges: None. Des Portes21,22, MP. Vado: None. These individuals have also been sequenced using long read technologies.First, STR calls were made at initial genome coverage of 100x or 300x using the recommended tool-specific set of reference STRs. Secondly, we downsampled the genomes to 30x-coverage and repeated our analysis.The number of genotypes calls made by Stretch varied by coverage from as low as 2310 (at 30x coverage) to ~16,000 (300x). De Rycke: None. Serhal: None. Darcan: None. In addition, in 8 patients in the genes LAMA2, COL5A1, CCDC78, COL12A1, MTMR14, variants of uncertain clinical significance were identified, which are the most promising from the point of view of converting them into probably pathogenic ones after additional studies. We further undermine loss-of-function as the pathomechanism and extend the phenotypic spectrum through a second case with epilepsy but without heart malformations. Prader-Willi syndrome is characterised by the loss of function of usually paternally expressed genes on a ~5Mb region of chromosome 15. MacCallum: A. Thyroiditis was diagnosed in 8/61 (13%) patients. Prins: None. Peruzzi: None. In this work, we use publicly available data repositories, such as the National Human Genome Research Institute GWAS Catalog, HUGE Gene Navigator, and the UK Biobank genetic and phenotypic dataset to gain insights into molecular pathways and individual genes behind a set of pregnancy-related traits. Introduction: BRCA1 and BRCA2 are the high-risk genes that are traditionally screened for germline mutations in the context of Hereditary Breast and Ovarian Cancer Syndrome (HBOC). P11.068.B Two distinct recessive conditions in two Pakistani sisters: molecular diagnosis using targeted gene panels may require subsequent whole exome sequencing in sibs of consanguineous parents FRANCESCA PELUSO 1, Stefano G. S.H. Banu: None. The identification of enhancers will help to understand how the expression of SCA genes is regulated in the human cerebellum and whether variation in these regions may lead to disease. Employment (full or part-time); Significant; Geneton Ltd.. Methods: We included 1,134 participants from the ALFA (ALzheimer and FAmilies) study. We previously described how GPs in the Netherlands met criteria for responsible implementation when offering this test to their patients. However, NGS analysis could be ineffective in identifying large and complex genomic rearrangements. Importantly, it takes the perspective of the clinician who has to integrate phenotypic and anamnestic data to assess the possibility of a hereditary disease. Patients with atypical presentations of the normal PTLS genotype or phenotype present a chance to better delineate the spectrum of the disease. Here we described two cases of PC harboring HRR mutations detected through a Next Generation Sequencing (NGS) multi-genes panel. The aim is to uncover known and novel cancer predisposing genes by reanalysing available whole-exome sequencing (WES) data of large cohorts in a combined manner, and applying a multidimensional omics approach. In this study we provide a first structured repository for BS, following FAIR data principles and data protection regulations, in order to facilitate comparisons and further clinical, genetic and AI-driven research. Kirmani: None. Results: We estimate that 0.8-1% of European couples are at-risk of having a child affected with a severe AR genetic disorder. Grant: CO: Italian Ministry of Education, University and Research to the DMM-University of Pavia "Dipartimenti di Eccellenza (2018-2022)" C. P.J. van der Sluijs 1, M. Picillo: None. Introduction: Developmental and epileptic encephalopathy-4 (DEE4) is a condition starting in infancy and characterized by abnormal brain function (encephalopathy), intellectual disability accompanied often by recurrent seizures. Vasilyev 1,2, Ekaterina N. While for both sexes, the genetic correlations on the X chromosome are comparable to the autosomal estimates. Introduction: It is estimated that 5-10% of breast and ovarian cancers (BC/OC) have hereditary origin. Deng: None. Both were recurrent mutations, previously associated with HPS type 1. The introduction of the NHS Rapid exome sequencing for acutely ill neonates and children (RAPS) in 2020, increased the need for urgent ward consultations. Keap1-Nrf2 pathway is the major regulator of cytoprotective responses to oxidative and electrophilic stress. Vieira Neto: None. Introduction: Genetic counseling and carrier screening of healthy candidates is part of gamete donors' selection. Patient 2 is a female with ataxia, intention tremor, and dyskinesia. However, it remains unclear whether such genetic variation is causally related to appendicitis risk. López-Fernández: None. We aimed to gain insights into the pathophysiological processes shared between T2D and four cancers through multi-phenotype (MP) genome-wide association study (GWAS). We further investigated CAG somatic expansions in normal (n ≤ 26), intermediate (n = 27-35) and reduced-penetrance (n = 36-39) alleles. Stoccoro: None. Evans: A. These loci were enriched for expression in brain tissue consistent with the known aetiology of ALS. Pina: None. Amelia Dobrescu 1, Alexandru Caramizaru2, Cristina Durac2, Raluca Tutunaru2, Andreea Catana3 1CRGM Dolj, UMF Craiova, Craiova, Romania, 2CRGM Dolj, Craiova, Romania, 3UMF Iuliu Hatieganu, Cluj, Romania. Raggio: B. Colonic mucosa biopsies were collected from 47 control individuals and 80 LS patients. Results: Frequency of heterozygous FTO-rs9939609 (p = 0.013) and COMT-rs4680 (p = 0.02), as well as homozygous 3R/3R MAO-A (p = 0.03) we significantly higher in girls with obesity. pneumoniae and S. A 58 gDNA sample panel was amplified using the NGSgo®-MX6-1 amplification strategy for HLA-A, B, C, DRB1, DQB1 and DPB1 (GenDx). F.L. Sciacca: None. C.W. Kirk: None. Gagua: None. Results: An average sequencing depth of up to 5,000x was achieved, allowing detailed evaluation of cancer-related transcripts. The re-study of unsolved cases showed a characterization yield of 63%, including 75% of monoallelic STGD cases in which a second pathogenic variant was found. Conclusions: the review highlights several relevant barriers to the application of pharmacogenomics in primary care, as well as factors that would facilitate the Introduction: These should be considered before introducing a pharmacogenomic panel in primary care. Teplyakova1, Tatyana P. Supported by RSF № 18-75-10046. These predictions were confirmed in vivo, and we correlated each structural cluster to different loss-of-function mechanisms: mutations in the catalytic pocket rendered a non-functional protein; mutations at the dimer interface led to unstable proteins; mutations in the β-sheet were highly unstable but retained some enzymatic activity. In addition, CMA identified a ~5 million bp heterozygous deletion, encompassing RBP3, within that locus. Desmet: None. Introduction: Sudden death in patients over 40 years old is commonly a result of asteroclerotic occlusion of coronary arteries. First, mutation of aromatic bulky Tyr to non-aromatic much less bulky Cys amino acid may inhibit the NARS homodimer formation or weaken the interaction between chains of the homodimer. M.S. Reuter: None. Renal cell carcinomas (RCCs) are a highly heterogeneous group of tumours derived from renal tubular epithelial cells, and together constitute the 7th most common cancer in the UK. Surprisingly, however, large PRKN rearrangements were also identified in a significant proportion (54%) of patients. All PPCD1 individuals were confirmed to harbour the same regulatory mutation in the OVOL2 promoter (NM_021220:c.−370T>C). Conclusion: The extension of single proband WES to trio analysis, HPOs prioritization, and recurrent updating of databases are essential to establish the definite diagnosis by discriminating causal variants among overlapping pathologies, discovering new genes, and changing variants categorization. Arslan Ates: None. T.V. Tregubchak: None. However, cell type heterogeneity within a tissue is an important source of variation of such endophenotypes and it has to be taken into consideration. We present the case of a patient with QS associated with FPLD. We aimed to check whether ULs with an apparently normal karyotype comprise "hidden" cell subpopulations with numerical chromosome abnormalities (heteroploid cells). Vorobey2, Valeriy V. Of these, 243patients(72.3%) presented pathogenic variant for PTPN11gene, 17patients(5%) for SOS1, 15 patients(4.4%) for RAF1, 9patients(2.6%) for SHOC2, 8patients(2.3%) for KRAS, 5patients(1.4%) for BRAF and 2patients(0.5%) for each of the genes MEK1,SPRED1,HRAS,NRAS and RIT1. Materials and Methods: 59 non recurrent, 17 recurrent PitNETS and 5 pituitary carcinomas were investigated for mutation and DNA methylation analysis in 15 and 32 driver genes respectively. We performed deep sequencing of mtDNA, defining haplogroups and evaluating private variants, including those at low heteroplasmy. Steina: None. No statistically significant difference was found between LINC01698 SNV rs75193730 genotypes and alleles. Targeted NGS screening can support the forensic investigation and help the cardiologist's decision to offer counselling and clinical evaluation to relatives of young SCD victims. Overall somatic dMMR was detected in 87.3% of dMMR tumors without germline MMR gene variants or MLH1-promoter methylation. A total of 3511 cases were retrospectively analyzed. MDLS is caused by microdeletions containing at least two genes, PAFAH1B1 and YWHAE, mapped on the 17p13.3 region, while isolated lissencephaly can result from heterozygous mutation or deletion of PAFAH1B1. Ben Zeglam: None. P16.007.B WINGS: Wales Infants and ChildreNs Genome Service. García-Mulero: None. Bonnevalle: None. Implication for diagnosis Roseli M. P09.007.D An apparently de novo Alexander-associated GFAP mutation transmitted from a healthy mother showing gonosomal mosaicism Alice Grossi, Tiziana Bachetti, Isabella Ceccherini Istituto Giannina Gaslini, Genova, Italy. Carrera: None. Introduction: Autosomal-dominant hypercholesterolemia (FH, OMIM#143890) is a common genetic disorder (1:250-1:500)1. Conclusions: We here present a dataset for interspersed repeats in coding regions of the human genome. N.V. Petrova: None. However, without identifying the origin human that provided the DNA contaminant, this can be difficult. The performance of these guide RNAs was tested on DNA from the NA12878 cell line. We would like thank Ms. Sukina Qanbar for her administrative support. Behavioral information was available for both parents of each proband. Differential expression showed downregulation of specific MLIP transcripts, those containing the LMNA interacting site and the NLS sequence; suggestive of a mislocalization and a loss of function. P04.054.C Four novel families expand the genotypic and phenotypic landscape of MESD-related Osteogenesis ImperfectaThao Tran1, Rachel Keller1, Brecht Guillemyn 2, Melanie Pepin1, Jane Corteville3, Samir Khatib4, Mohammad-Sadegh Fallah5, Sirous Zeinali5,6, Fransiska Malfait2, Sofie Symoens2, Paul Coucke2, Peter Witters7, Hamideh Bagherian4,5, Deborah Nickerson1, Michael Bamshad1, Jessica Chong1, University of Washington Center for Mendelian Genomics, Peter Byers1 1University of Washington, Seattle, WA, USA, 2Ghent University, Ghent, Belgium, 3Case Western Reserve University, Cleveland, OH, USA, 4GMDC Al Quds University, Al Quds, Palestinian Territory, 5Kawsar Human Genetics Research Center, Tehran, Iran, Islamic Republic of, 6Pasteur Institute of Iran, Tehran, Iran, Islamic Republic of, 7University Hospital Leuven, Leuven, Belgium. Minor dysmorphic features were observed, although neither the individuals' facial nor general appearance were obviously distinctive. Conclusion: The karyotyping, FISH- and bioinformatic analysis revealed that the initial NGS-based diagnostic of a 9p triplication turned out to be a complete tetrasomy 9p with an additional isodicentric chromosome. The new disease was added into the McCusick international database under the OMIM number # 617303 and named mucopolysaccharidosis-plus syndrome (MPS-PS). Four subgroups were created based on deletion sizes. All tested children were good candidates for CI as their HL causative genetic variants are localized in genes preferentially expressed in the cochlea. Introduction: Mitochondria are involved in different key aspects of cell homeostasis. Perhaps, allelic heterogeneity in Cowden syndrome determines the clinical polymorphism of the disease, and the molecular genetic analysis by NGS allows to clarify the diagnosis and to counsel affected families on the possibilities of prenatal diagnosis and risk of fetus pathology. A statistically significant difference revealed among two groups women for genotype frequencies of STAT3 GG / IL12B 1188CC / IL-10 -1082GA. P10.049.A María Fenollar-Cortés 1,2, Carmen Cotarelo-Pérez1,2, Raluca Oancea-Ionescu1,2, Alejandro Horga3,2, Antonio Guerrero-Sola3,2, Lucía Galán-Dávila3,2, Clara Herrero-Forte1,2 1Unidad de Genética Clínica. Brittle cornea syndrome is a rare syndrome, characterized by extreme thinning of cornea with estimated prevalence less than 1 in 1,000,000. Rieubland: None. Library and template preparations were performed using the automated Ion Chef System, then sequenced in Ion S5 with Ion 520 Chip according to the manufacturer's instructions. To study epidermal pathobiology, we generated permanent human keratinocyte cells (HaCaT) stably expressing wild type HRASWT or CS-associated HRASGly12Ser and screened for keratinocyte-specific HRAS binding partners by affinity purification and quantitative mass spectrometry. Over the years, CACNA1A has been associated with a broader spectrum of phenotypes including epilepsy, intellectual disability, and neurological episodic syndromes during childhood. Introduction: In the past years, somatic mutations affecting H3F3A and H3F3B genes coding for Histone 3 variant H3.3 have been established as well-known drivers for tumour development. KCNB1 mutations are known to cause global developmental delay, behavioral disorders, and various epilepsies. Conclusion: There are ACE2 and AGTR1 polymorphisms that could influence severity of phenotype Covid-19 and, moreover, it depends on gender and the presence of comorbidities. Data on serum TTR levels are available for 100 of them. One mother revealed a mosaicism of the GFAP mutation already detected in her son. In conclusion, we are highly suspicious that the de novo variants in the candidate gene TNRC6A are clinically relevant, however, additional cases with overlapping findings and functional studies are needed to reach more solid conclusions. Despite the clinical importance of distinguishing between gestational and non-gestational trophoblastic tumours, which vary in their prognoses and treatment regimens, tumour biopsies are not always available for genotyping due to the risk of haemorrhage. Polygenic risk scores (PRS) represent a quantification of the individual genetic predisposition with respect to a given phenotype. 0.028, P = 2.35e-18) manifested in an increased genome-wide burden of long-sized (>3.227 Mb) regions of homozygosity (ROHs) (114.24 vs. Oliveira: None. In 250 (89.3%) families, the index case had NDD. Mortality is high among the severely affected patients, while SC phocomelia individuals usually survive to adulthood. Interestingly, whole exome sequencing revealed a promising candidate involved in the nucleo-cytoplasmic trafficking. Conclusions: Our automation approach successfully created sequencing-ready libraries while minimizing manual pipetting, handling errors and manual touchpoints. The research was funded by RFBR according to the project № 18-29-14073. Maede: None. California Center for Rare Disease: None. Using this approach, we have detected a mosaic TGFBR2 variant (VAF of 20%) in a clinically unaffected individual with multiple children with Marfan syndrome. Assmann: None. We applied this platform to study the genomes of multiple constitutional disorders. In February 2018, the result of tissue biopsy detected two mutations, APC p.Gln1406* (55.2%) and TP53 p.Asn239Asp (58.0%). Szatmari: None. Patients and methods: Tumour samples from 177 patients included in the clinical trial TTCC-2007-01 were used. Salnikova1,2 1Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology, Moscow, Russian Federation, 2Vavilov Institute of General Genetics, Russian Academy of Sciences, Moscow, Russian Federation, 3Dmitry Rogachev National Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russian Federation, 4Weizmann Institute of Science, Rehovot, Israel. Schwartzmann: None. Albayrak: None. Materials and Methods: Phenotips was used for an accurate and standardized description of phenotypes (through HPO, Human Phenotype Ontology). El-Kamah: None. The glycaemic cluster highlighted 28 T2D SNPs with effects on glycaemia. The child exhibits autistic behavior. Bertrand: A. Mutations in genes which encode proteins involved in the lectin complement pathway MASP1, COLEC11 and recently COLEC10 have been identified in patients with 3MC syndrome, supporting their role during human development. Materials and Methods: Thirty SNPs associated with Alzheimer's disease and schizophrenia were genotyped by MALDI-TOF mass-spectrometry using MassARRAY Analyzer 4 (Agena Bioscience) in sixteen populations of North Eurasia (Russians, Udmurts, Kazakhs, Uzbeks, Kyrgyz, Yakuts, Kets, Northern Altaians, Southern Altaians, Evenks, Buryats, Khants, Tuvinians, Khakass, Chukchi, Nivkhs, Koryaks). However, while CCHS is a Mendelian disorder, ALTE and SIDS are complex traits, where common genetic variants, together with external factors, may exert an additive effect with symptoms likely manifesting only over a "threshold". O'Sullivan: None. Chruszcz: None. MO knockdown of plxna1a and plxna1b in zebrafish larvae resembled the human CNS and eye phenotype. Santos-Mata: None. Methods: The survey involved 370 obese children and adolescents from 3 to 17 years old with a body mass index (BMI > 30), as well as 123 children and adolescents of the same age without obesity (BMI ˂ 20). Our expectation is that this cohort will significantly expand in the short term, as awareness for this clinical entity increases. R.J. Rodenburg: None. P10.017.A systematic analysis of genetic variation of duchenne muscular dystrophy and implication for cancer Hubert Chen Ivymind Academy, West Windsor, NJ, USA. Exon 19 appeared to have most density of pathogenic SNP distribution. Balcere: None. In the Bedouin community in Israel, consanguineous marriages are common, contributing to high rates of congenital malformations and genetic diseases. Mutarelli: None. Support for inclusion of the Primary Findings section was high (96%) but fewer respondents agreed to include the Secondary Findings (71%) and Incidental Findings sections (58%). Methods: Since 2015 at our institute, the individuals fulfilling the HBOC testing criteria were counseled and screened for germline PVs in NCCN-HBOC genes by Illumina's NGS multigene panel. LOC105375120 genotype G/G frequncy was 57,9 % in patient group compare with 28,6 % control group (p 10 000 U/L) with painful muscles. Palazzo: None. Shabani: None. G.V. Harlalka: None. Introduction: Monogenic diseases play an important role in critically ill neonates and infants treated in the intensive care unit (ICU). However, the liquid biopsy showed no abnormalities. Ulys: None. Data analysis and variant reporting was performed with the SeqArray software (JSI, Germany). Ivanov1, Polina I. P20.043.B SV detection, SNP phasing and haplotype methylation calling from one nanopore sequencing dataset provides insights to complex genomic disorder Heather Mary Jeffery, Philipp Rescheneder, Daniel Turner, Phillip James, Sissel Juul Oxford Nanopore Technologies, Oxford, United Kingdom. This alteration is either paternally inherited or de novo. Methods: 427 participants (205 in general population and 222 students, with different study domains) were recruited. After the analysis, a subset of 14 miRNAs was selected -8 upregulated (miR-18a-5p, miR-181a-5p, miR-181b-5p, miR-21-3p, miR-24-3p, miR-93-5p, miR-210-3p, miR-1246) and 6 downregulated (miR-140a-3p, miR-145-5p, miR-148a-5p, miR-204-5p, miR-497, miR-874-3p). P12.105.A Sequential somatic HRAS mutation and gene duplication in a patient with epidermal nevus and rhabdomyosarcoma: further evidence of a two-hit pathogenetic mechanism contributing to oncogenic transformation Roberta Zuntini 1, Lucia Pedace2, Evelina Miele2, Stefano Giuseppe Caraffi1, Stefano Gardini3, Elena Ficarelli3, Riccardo Pampena3, Simone Pizzi4, Francesca Clementina Radio4, Angelica Barone5, Simonetta Piana6, Patrizia Bertolini5, Domenico Corradi7, Maria Marinelli1, Alberico Motolese3, Marco Tartaglia4,8, Livia Garavelli1,8 1Medical Genetics Unit, AUSL IRCCS Arcispedale Santa Maria Nuova, Reggio Emilia, Italy, 2Department of Pediatric Hematology/Oncology and Cellular and Gene Therapy, Ospedale Pediatrico Bambino Gesù, IRCCS, Roma, Italy, 3Dermatology Unit, Azienda USL, IRCCS, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy, 4Genetics and Rare Diseases Research Division, Ospedale Pediatrico Bambino Gesù, IRCCS, Roma, Italy, 5Pediatric Hematology Oncology Unit, University Hospital of Parma, Parma, Italy, 6Pathology Unit, Deptartment of Oncology and Advanced Technologies, Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy, 7Unit of Pathology, Department of Medicine and Surgery, University of Parma, Parma, Italy, 8, These authors jointly coordinated this work, Italy. „Gain of function" variations and duplications were the predominant type of genetic defect we found. Low NGS sequencing yield can arise in these regions due to the presence of various repeat elements or biased base composition while inaccurate mapping can result from segmental duplications. As such, it assesses the perceived decision support patients received during genetic counseling. Preliminary results show that both AdaSub with the extended Bayesian information criterion for variant selection (EBIC) and SBP reach a better accuracy than univariable clump-based PRS (cPRS) while including a small number of variants (height RMSE = 8.928;8.755;8.951; variants in the final model = 292;7668;26184, LDL RMSE = 0.827;0.823;0.841; variants in the final model = 105;761;1660, values are for EBIC1, SBP and cPRS respectively). P07.011.C A case report of an atypical FIP1L1-PDGFRA fusion in a patient with hypereosinophilia Sadiye Ekinci 1, Güldane Cengiz Seval2, Halil Gürhan Karabulut1, Arzu Vicdan1, Seher Yüksel3, Işınsu Kuzu3, Günhan Gürman2, Timur Tuncalı1 1Department of Medical Genetics, Ankara University Faculty of Medicine, Ankara, Turkey, 2Department of Hematology, Ankara University Faculty of Medicine, Ankara, Turkey, 3Department of Pathology, Ankara University Faculty of Medicine, Ankara, Turkey. Analysis included SNVs, copy number variants and uniparental disomy. This study shows how a patient-friendly first trimester screening for both chromosomal and structural fetal anomalies in only two outpatient visits can be provided. Sanchez Bueno: None. P23.018.B Legal regulation of human genome editing in the Russian Federation Andrey A. P10.016.D Isoform specific variant as a potential cause of distal myopathy Jean Mezreani 1,2, Florence Martin1, Sébastien Audet1,2, Jade Charbonneau1, Erik Bareke1, Annie Laplante1, Bernard Brais3,4, Erin O'Ferrall3,4, Jason Karamchandani3,4, Martine Tétreault1,2 1CRCHUM, Montreal, QC, Canada, 2Neurosciences Department, UdeM, Montreal, QC, Canada, 3MUHC, Montreal, QC, Canada, 4Rare Neurological Diseases Research Group, Montreal, QC, Canada. Löhr: None. In 78% of diagnosed cases, the casual variant corresponded to a de novo mutation. 83% were undergraduate; 61% were not married, 87% did not plan conception in the near future, 6% had relatives with hereditary diseases. We showed that our pipeline could be used to identify rare GPV that lead to HRD, but our results suggest that in French Canadians it is unlikely that a significant fraction of unexplained multi-case families is due to HRD-associated variants. Meašić: None. S.G. Temel: None. Grant support: National Institute of Health (1R01CA218342-01A1) C. Methods: Protein structure prediction of MLH1 variants were constructed using Phyre and I-TASSER protein modelling tools. For personality traits, mean scale of PL was significantly higher in homozygous AA rs9939609-FTO girls (p = 0.001) whereas mean scale of PH was significantly higher in homozygous boys (p = 0.034). Sequenced data was analyzed using Qiime2 and phyloseq packages. We present a new pathogenic mechanism in line with this observation. Due to the long length of the assembled maps, large structural variants (SVs) can be captured by aligning to the public human reference assembly. In this study, we aim to gain insight on the disease impact of BMI associated genetic variants mediated by their expression in different tissues. Witkowski: None. Vos1, Cleo C. The diagnosis of these disorders is often challenging due to the complexity of the clinical and neuroimaging features of these malformations, the rarity of the individual disorders or phenotypes, as well as the rapidly expanding genetic landscape; the identification of which is primarily due to the increasing use of Next Generation Sequencing (NGS) methods. Gene-panel sequencing revealed a splicing variant c.701+1G>A in TBK1. Efthymiou: None. Maystadt*: None. Identification and interpretation of these variants is challenging, leaving many patients without molecular diagnosis. Martinez-Monseny: None. P07.024.D PADI4 and PADI2 enhance collagen-initiated inflammatory responses Akari Suzuki, Takumi Shibuya, Kazuhiko Yamamoto RIKEN, Yokohama, Japan. Our results suggest a critical role of CYR61 in the regulation of body composition, possibly mediated by angiogenesis and adipocyte growth. Bauer: A. Parents karyotype were normal. Pedace: None. The genetic evidence in the family and functional experiments in chick embryos indicate that the homozygous pathogenic variant in CDC25B are likely the cause of a recessive syndrome with short stature, microcephaly, severe intellectual disability and developmental delay. P12.015.C Clinical practice guidelines for BRCA1 and BRCA2 genetic testing Marion Imbert-Bouteille 1, Massimo Barberis2, Philip Beer3, Eitan Friedman4, Josep M. Komatsuzaki: None. Conclusions: We present a wide series of NS cases with clinical manifestations, mostly, in accordance with previous publications. Urbanczyk: None. Heath3,4,5, Jesus Pozo-Roman6,7,8, Maria Angeles Santos-Mata9, Elena Artola10, Guiomar Perez de Nanclares1 1Rare Diseases Research Group, Molecular (Epi)Genetics Laboratory, BioAraba Health Research Institute, OSI Araba, Araba University Hospital-Txagorritxu, Vitoria-Gasteiz, Araba, Spain, 2NanoBioCel Research Group, Laboratory of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of the Basque Country UPV/EHU, Vitoria-Gasteiz, Araba, Spain, 3Institute of Medical and Molecular Genetics (INGEMM), La Paz University Hospital, Autonomous University of Madrid, IdiPAZ, Madrid, Spain, 4Skeletal dysplasia Multidisciplinary Unit (UMDE), La Paz University Hospital, Madrid, Spain, 5CIBERER, ISCIII, Madrid, Spain, 6Departments of Pediatrics and Pediatric Endocrinology, Hospital Infantil Niño Jesús University Hospital, Autonomous University of Madrid, Madrid, Spain, 7La Princesa Research Institute, Madrid, Spain, 8CIBEROBN, Institute of Health Carlos III, Madrid, Spain, 9Pediatric Endocrinology Unit, Paediatric Service of the University Hospital de Jerez, Jerez de la Frontera, Cádiz, Spain, 10Paediatric Department, Donostia University, Donostia, Gipuzkoa, Spain. However, little is known about its function in GBM. We present recent enhancements including: focused expansion of Mammalian Phenotype ontology terms enabling enhanced and refined retrieval of coronavirus-relevant model phenotypes and genes; a redesigned page display; and sort/filter functionality facilitating analysis of customized datasets by model design or research application. Modified OTDDNs, upon random incorporation during primer extension reaction, create DNA fragments of a desired average length, with simultaneous labeling of a corresponding DNA strand with sequencing adapter. Materials and Methods: In this study, FISH results and clinical data for CML-CP patients (n = 83) treated in the period 08/2005-12/2019 in the Federation of Bosnia and Herzegovina were evaluated. Yilmaz: None. We propose that ZFHX4 loss-of-function is associated with an autosomal dominant condition, characterized by a neurobehavioural phenotype and a recognizable pattern of facial features. The frequency of PAVs with CADD score ≥ 30 was significantly higher in ASD patients, compared to controls (P = 0.0042). However registered users can record ACMG classifications for the variants, and trigger the automated submission of the variant to the Global Variome Shared LOVD instance, ensuring a persistent sharing of the variants. Germline heterozygous POLE or POLD1 pathogenic variants (PVs) cause PP associated polyposis (PPAP), presenting with colorectal adenomas and carcinomas in adulthood. Okamoto: None. Among these variants, we focused our attention on the heterozygote mutation R266W, that could have a deleterious consequence for the protein structure perturbing its function. Bartakke: None. Conclusions: Two novel missense mutations p.Leu153Pro, p.Ile151Asn and p.Glu70Lys mutations are related exclusively to retinal and cerebellar haemangioblastomas, while p.Arg176fs mutation phenotype includes also phaeochromocytoma. Kaur: None. Kamoun: None. Darling: None. In 53% (38/72) the diagnosis was made post-neonatally (median age = 209 days) using assays including exome sequencing. Within six years, the patient progressively developed a bilateral pyramidal syndrome, mild wearing-off, and dyskinesias. Wada: None. Results are marked by wide discrepancies, such as in motivation (meeting DTC demand in a hospital setting vs. Geelen: None. The serum K-level was 2.3-2.5 mmol/l (normal 4.1-5.3 mmol/l). Dey: None. Chemiluminescence was used to detect fast flash values and by using real time PCR was detected ct values. Materials and Methods: We scanned the human reference genome for all repeat sequences of a length ranging from 7-20bp, separated by a maximum distance of 1000bp. The report could expand clinical features of this condition and help to define natural history of the disease. A.V. Predeus: None. Alatwi: None. van Tintelen: None. P10.037.A Cis MFN2 missense variants causing familial CMT2A2A Enrica Marchionni 1, Fabiana Fattori2, Gioia Mastromoro1, Daniele Guadagnolo1, Francesca Di Palma1, Luca Bosco2, Enrico Bertini2, Antonio Pizzuti1 1Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy, 2Unit of Neuromuscular and Neurodegenerative Disorders, Department of Neurosciences, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy. Extracellular matrix protein-1 (ECM1) encoded by ECM1 gene is involved in differentiation of keratinocytes by binding to structural proteins, and angiogenesis. Upadhyai: None. Although telegenetics has been accepted and applied, especially in a pandemic time, major part of both participants and providers of CG prefer face-to-face communication. Focus formations assays were performed on NIH3T3 cell lines transfected with MET p.(Leu1130Ser). Familial and clinical informations were collected from medical records. Methods: Array-CGH analysis was performed by a CGXTM HD v1,1 4-plex array 180 k (PerkinElmer), with an average resolution of 40 kb in the backbone and 20 kb in the regions of interest. Index 3 was clinically conspicuous for CF at the age of 2 years with failure to thrive and severe exocrine pancreatic insufficiency. Hall 1, Rachel Hart2, Angus Clarke3 1PHG Foundation, Cambridge, United Kingdom, 2West Midland Region Clinical Genomic Centre, Birmingham Women's and Children's Hospital, Birmingham, United Kingdom, 3School of Medicine, Cardiff University, Cardiff, United Kingdom. Exome sequencing revealed a heterozygous de novo frameshift-mutation in the SETD5 gene. Boguszewska-Chachulska: None. Our results showed 5 known variants in C20orf54 gene both in the proband and in healthy family members (I74M in exon 2 and P267L, T278M, I303V, R266W in exon 3). Mařík: None. M.E. Melendez: None. α-tropomyosin is an α-helical coiled-coil dimer that spans the actin filament's length as a co-polymer. Whole-exome-sequencing was performed via XGEN. Chiodi: None. Filby: A. Results: Meta-analysis showed no association of TNF-α(G308A) but a strong association of MTHFR(C677T) with high FGR risk (OR = 1.22, 95 % CI: 1.07-1.39, P = 0.002). Rovite: None. P.E. Umriukhin: None. Prokofev3 1Research Institute of Biology, Rostov-on-Don, Russian Federation, 2academy biology and biotechnology, Rostov-on-Don, Russian Federation, 3Southern Federal University, Rostov-on-Don, Russian Federation. M.K. Rai: None. All rights reserved. Stephan: None. We performed a single rare variant analysis (MAF T and NM_153427.2:c.408_410delTCG) and one described earlier (NM_153427.2:c.191C>T). The current questionnaire consists of 41 multiple-choice questions exploring physical parameters, cognitive and behavioural aspects, presence or absence of neurological manifestations or problems affecting major physiological functions (cardiac, respiratory, renal...). establishing biobanks), envisioned target groups (PCG as universal population screening vs. Consultant/Advisory Board; Modest; Diaceutics, The Science Advisory Board. Assay Workflow• gDNA was sheared using a Covaris g-TUBE into 8kb fragment sizes.• Fragmented 8kb gDNA was used to generate an 8-point 2-fold standard curve.• 100 ng/μL, 50 ng/μL, 25 ng/μL, 12.5 ng/μL, 6.25 ng/μL, 3.13 ng/μL, 1.56 ng/μL, 0.78 ng/μL AnEcho Qualified Acoustic Tube was filled with 50 μL of each standard curve dilution point.• 0.5 μL gDNA was transferred using an Echo 655T to a 9.5 μL qPCR reaction. Despite many different software tools to support analysis, the diagnostic yield is still limited to 20-70%, depending on the phenotype. The genome data has been searched for genomic variation represented in this population, and a number of variants have been reported: large structural variants, indels, CNVs, SNPs and microsatellites. Yet, small individual patient cohorts and the lack of standardized phenotype information hinder the complete elucidation of these genetic disorders. Whole-genome sequencing and smell phenotypes data of 218 Italian individuals allowed the identification of 41 natural OR knockouts (KO) (i.e., genes carrying biallelic loss of function variants). Maniatis: None. Putoux: None. We aimed to explore RE activity in chronic lymphocytic and acute lymphoblastic leukemias, and myelodysplastic syndrome. Modifier genes and epigenetic factors play important roles in determining the severity of disease. Wan: None. Introduction: Due to the high prevalence of obesity-related diseases, the importance of researching the relationship between gene polymorphisms and obesity does not lose importance. We detected C5 mutations in colorectal cancer (3 samples carried APC and TP53 mutations), 2 C5 and a C4 mutation in melanoma. Tyr163Asn, p. Godron: A. Fernandes, Ana L. Introduction: Genetically and clinically heterogeneous left ventricular non-compaction (LVNC) is the third most frequent cardiomyopathy in the pediatric population. Genotyping was performed through fragment and RP-PCR analysis. Bostan: None. Our goal was to establish the founder effect of this alteration and characterized its associated clinical phenotype. Colleaux: None. Müller-Brochut: A. These findings build on our multiplexed long-read sequence analysis of a 69bp intronic repeat in WDR7 in >300 individuals, which revealed multiple origins of the repeat that have continued to expand in a directional manner. Novel candidates discrete to individual kindreds included a frameshift variant in CNTNAP3 (tumour CNV loss in both affected family members), a missense variant in LMNB2 (tumour CNV loss concordant in 1/3 siblings), and a missense variant in GAPVD1 (CNV loss and LoH in both affected family members). Introduction: Type-IV-collagen-related nephropathy covers a spectrum of hereditary hematuric diseases (thin basement membrane nephropathy, TBMN; Alport syndrome, AS). Barreda-Sánchez: None. P09.011.D Alzheimer's disease polygenic risk score assessment on longitudinal amyloid load in cognitively intact older adults Emma Susanne Luckett 1, Jolien Schaeverbeke1, Lars Bertram2, Koen Van Laere1,3, Patrick Dupont1, Isabell Cleynen1, Rik Vandenberghe1,3 1KU Leuven, Leuven, Belgium, 2University of Lübeck, Lübeck, Germany, 3UZ Leuven, Leuven, Belgium. W.M. Schmidt: None. Schrøder4, Morten Frost2, Moustapha Kassem2, Lilian B. To gain further understanding of the molecular epidemiology of the outbreak in Azerbaijan, a full-genome sequencing was performed on nine SARS-CoV-2 isolates. Heterogeneity of extracutaneous manifestations and high incidence of sporadic cases were observed in our cohort with IP. Fealey: None. A significant inverse correlation between pyrosequencing D-loop methylation levels and age at sampling of the individuals enrolled has been detected (r = -0.53, p T: p.Arg522*) at exon 17 and one intronic variant NM_001354906.2:c.-191T>A. Additionally, applying these methods to real medical data demands a previous formalization phase. 70.4%, microcephaly (63.6%) and strabismus (68%). Al-Muhaizea: None. Genome wide association study was performed to investigate the genetic background of following phenotypes: diabetic neuropathy, diabetic nephropathy, macrovascular events, and ophthalmic complications. Introduction: Hereditary hearing loss (HHL) is a genetically heterogeneous group of disorders. With these concepts as a starting point, a description of a possible complementary course on relevant philosophical concepts is proposed with the aim of providing genetic counsellors with adequate philosophical tools for ethical genetic counselling. Chromosomal microarray showed a microdeletion of NAXD exons 1-2, and exome sequencing revealed a novel NAXD SNV predicted to affect both a splice donor site and the mitochondrial pre-sequence tag but leaving the NAXD endoplasmic reticulum and cytosolic isoforms intact. Amor-Barris: None. Nasedkina1,3 1Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Moscow, Russian Federation, 2N.N. Blokhin National Medical Research Center of Oncology, Moscow, Russian Federation, 3Dmitry Rogachev National Medical and Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russian Federation. Yet, it is largely unknown if specific features of brain morphology and behaviour have a shared genetic architecture. Quintana-Luque: None. These data refine the size of the duplication at the 22q11.21 also suggesting that CRKL, THAP7, and LZTR1 are CBE candidate genes and contribute to the potential disease-associated mechanism predisposing to BEEC at this locus. C.M.P.C. Peeters-Scholte: None. The ongoing COVID-19 pandemic exemplifies the need for new tools and methods to elucidate the mechanisms of viral infection, pathogen-host responses, and diversity in cellular responses to infection. Patients at the highest wGRS39 tertiles had OR > 1.62 for having CeD-related symptoms during childhood, severe small bowel mucosal damage, malabsorption, anaemia. Levy 1, Mathis Hildonen1, Christina Dahl2, Victoria A. The corresponding genes were further analysed in qRT-PCR and their expression was found to be deregulated. Among the 300 genetically diagnosed patients, the clinical diagnosis was confirmed in 77%, a specific diagnosis within a clinical diagnostic group was identified in 15%, and 7% of cases were reclassified. Results: CFTR sequencing was performed for all three siblings: two older siblings with classical CF phenotype had 1677delTA and I1234V variants (both classified as "CF" alleles), whereas younger sibling had 1677delTA and L997F variants (classified as "CF" and "risk factor" alleles respectively). Songolova: None. Michailidou: None. The study sized 14 men and 11 women, 88% of the patients were diagnosed with advanced stages T3-T4. Clinical acumen and an integrated testing approach are the key to a successful diagnosis. Additionally, we searched the literature for previously reported cases of either PHS, GCPS or isolated polysyndactyly with confirmed mutations in the GLI3 gene. Results: The most abundant genera detected in saliva were Prevotella, Streptococcus, Haemophilus, Veillonella, Neisseria, Rothia, and Fusobacterium. Introduction: Spontaneous abortion (SA) occurs in 10-15% of clinically recognized pregnancies and recurrent pregnancy loss (RPL) in 1-3%. No gene mutations were detected in the mother or father. In our final model, we demonstrated that repeats within the contact zone are 3-times more mutagenic as compared to repeats outside the contact zone, which clarifies also well known increased mutagenicity of the common repeat (8470-8482 bp and 13447-13459 bp). K.J. Jensen: None. Here we present serendipitous genetic findings that identify SCN9A c.1921A>T p.(Asn641Tyr) at high frequency among the Amish, in the absence of seizure phenotypes. Frétigny: None. A list of 20 concepts was elucidated including genetic determinism, essentialism, reductionism, as well as philosophical trends: principialism, ethics of care, personalism. In 86 of 95 individuals, the IF was medically actionable. P19.041.A Identification of genetic variants associated with blood miRNA expression levels in childrenGeòrgia Escaramís1,2, Marta Vives-Usano3,4,5, Carles Hernandez-Ferrer3,4,5, Léa Maitre3,5,2, Sandra Andrusaityte6, Àngel Carracedo7,8, Maribel Casas3,5,2, Leda Chatzi9, Regina Grazuleviciene6, Kristine B. Kocheva: None. Brittle cornea syndrome (BCS) is a rare autosomal recessive disorder characterized by corneal thinning and fragility, leading to corneal rupture, the main hallmark of this disorder. Results: A total of 37 Danish cases and 60 published cases were included. In this study we analyzed phenotypes of CF individuals with TT and CC genotypes of MTHFR gene.

Clinical observation: A 38-year-old Libyan patient was referred to our genetic counseling because of a colorectal cancer. Charzewska: None. Koskenvuo: A. P22.030.A An innovative e-training tool for the clinical management of NDD, the DefiGame serious game Anne Hugon 1, C. Introduction: Genome-wide androgenetic mosaicism is a rare condition in which two euploid cell lines coexist in the same individual, one with biparental content and one with genome-wide paternal isodisomy. Conclusion: Variants were analyzed by means of a global study of genetic variants in several databases, protein structure and protein stability to determine their possible effects and their correlation with patients' phenotypes. We demonstrate a workflow for DNA isolation from bone marrow aspirates or peripheral blood, data collection, variation/abnormality calling, and annotation. Fortuna1, Natália Tkachenko1 1Centro de Genética Médica Jacinto Magalhães, Porto, Portugal, 2Centro Materno Infantil do Norte, Porto, Portugal. Candido-Souza1, Roseli M. 30-70% is explained by a large coding copy number variation ("KIV-2 repeat") encompassing up to 70% of LPA. P06.046.C Revisiting clinical presentation of Egyptian patients with mucopolysaccharidoses Solaf Elsayed 1, Rabah Shawky1, Walaa Yousef2, Abdullah Abdullah1 1Medical Genetics Department, Faculty of medicine, Ain Shams University, Cairo, Egypt, 2Pediatrics Department, Faculty of medicine, Ain Shams University, Cairo, Egypt. The majority of non-BRCA variants were found in ATM and in MMR genes. P11.005.C Neonatal diagnosis of 16p12.2 microdeletion syndrome Pamela Paglia 1, Mariateresa Falco2, Dario Di Salvio3, Piero Pignataro4, Anna Rita Frascogna5, Maria Grazia Corbo5, Rita Genesio4, Daniela Melis1 1Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", Section of Pediatrics, University of Salerno, Baronissi (SA), Italy, 2Clinical Pediatrics, University Hospital "San Giovanni di Dio e Ruggi D'Aragona", Salerno, Italy, 3Department of Translational Medical Sciences, Section of Pediatrics, University of Naples "Federico II", Napoli, Italy, 4Department of Molecular Medicine and Medical Biotechnology, University of Naples "Federico II", Napoli, Italy, 5Department of Maternal-Infant, Neonatology and Intensive Care Unit, University Hospital "San Giovanni di Dio e Ruggi D'Aragona", Salerno, Italy. Introduction: Cornelia de Lange Syndrome (CdLS) is a rare genetic disorder classically characterized by distinctive facies, growth retardation, intellectual disability, feeding difficulties, and multiple organ system anomalies. Conclusions: These results encourage the optimization of these practices in the long term. Functional analysis of the identified variants is an important step to interpret the clinical consequences of genetic variants and search for specific treatment for GRIN-related neuropathologies. Variants in TLK2 were associated with "Mental Retardation Autosomal Dominant 57" (MRD57), a neurodevelopmental disorder characterized by a highly variable phenotype, including intellectual disability, behavioral abnormalities, facial dysmorphisms, microcephaly, epilepsy, and skeletal anomalies. Spano: F. Mingrino: None. No significant association between LTF rs#1126478 variant, and risk of dental caries was observed. Finally, high hs-MSI levels were found in 1/7 colonic polyps, while the presence of MMRd-crypts were identified in colon mucosa from 2/17 LS patients, persisting in a subsequent colonoscopy biopsy of one of them. The sharing of genetic information within the family and with clinicians was not deeply explored so far; information inferred from family history was not addressed as well. Four missense variations were not previously reported and were considered of unknown significance. P12.040.D Complex karyotype in the course of CLLDorota Koczkodaj1, Małgorzata Luterek1, Zuzanna Dołżycka 1, Ewa Wąsik-Szczepanek2, Agata Filip1 1Department of Cancer Genetics, Medical University, Lublin, Poland, 2Department of Hematooncology and Bone Marrow Transplantation, Medical University, Lublin, Poland. Methods: The study enrolled and characterized through ctDNA droplet digital PCR (ddPCR) 49 women with Luminal MBC. It is genetically heterogenous, with variants in 30 genes implicated, many also associated with anophthalmia and microphthalmia. Methylation-sensitive restriction enzyme coupled qPCR (MSREqPCR) has been setup to test the diagnostic performance in plasma cell-free DNA (cfDNA) of candidate markers deduced from CRC tissue. Furthermore, we developed a method for detection of UPDs in WES-solo cases and recently integrated it into the diagnostic pipeline. P09.122.C Proteomics of the dentate gyrus reveals semantic dementia specific biology Merel O. Tops3, Maartje Nielsen3, Dennis K. No. RFMEFI60518X0003. Methods: We have collected clinical and genetic data from individuals with a germline loss-of-function SMARCA4 alteration through all Dutch DNA diagnostic laboratories. Surprisingly, we identified 35 (6%) cell lines that better matched a different tissue type than the one they were originally annotated with, both by transcriptome and epigenome. Giliberti: None. Working with human chromosomes rather than DNA was very popular in the 1970s/1980s. Introduction: More than 50% of early pregnancy losses have a chromosomal abnormality. Caporaso, Nehal N. P11.028.B Identification of Cenani-Lenz syndrome due to compound heterozygous variant in APCJair A. Kchouk: None. Conclusions: Statisticaly significant higer frequency was determinated of SNV SPRR2C rs2291979 A allele and LOC105375120 G/G genotype and G allele compare with control group. Vita: None. W.R.R. Geurts-Giele: None. Eighteen offspring of twelve families have earlier been sequenced on a HiSeq X, three of which have now been resequenced. Rubio Martín: None. Mazaheri: None. Ata: None. The mutated genes belonged to the group of genes associated with epilepsy syndromes/epileptic encephalopathy. The Chromosome 6 Project collaborates with parents to study the phenotypes of chromosome 6 aberrations. Employment (full or part-time); Significant; Bionano Genomics. Soria: None. Introduction: It is known that alteration of several genes associated with skeletal disorders could lead to multiple, highly variable phenotypes. At 5% FDR, we discovered 10'111 and 5'152 TE-eQTLs as well as 6'856 and 1'539 gene-eQTLs in normal and tumor samples, respectively. Participants reported rare diagnosis status in addition to COVID-19 symptoms, test results, and level of care required following COVID-19 diagnosis. Koellinger: None. In total, we investigated four potential splice site variants in TCF12 and FGFR2. In this study, we describe the clinical manifestations and disease course in an additional six Saudi patients whose blood samples were assessed by Affymetrix's axiom autozygosity mapping, and whole exome sequencing. Results: Case1 - A female genomic profile was detected with a loss in homozygosity (zero copies) in 7p21.2p21.1 of 360 Kbp involving the CRPPA, CRPPA-AS1 and SOSTDC1 genes. Conclusions: The results obtained in this study may indicate the contribution Notch signaling pathway gene alterations to the pathogenesis of clear cell renal cell carcinoma, as well as the possibility of their use in creating a molecular markers panel for the diagnosis and prognosis of the course of the disease. Other Research Support (supplies, equipment, receipt of drugs or other in-kind support); Modest; Fluent BioSciences. In conclusion, we identified 4 variants in genes encoding proteases (FURIN, PLG and PRSS1) and 6 in genes involved in the innate immunity (MBL2 and OAS1) that might be relevant for the host response to SARS-CoV-2 infection. Most represent de novo cases detected by trio-whole exome sequencing (trio-WES). Dhaenens: None. One patient had accessory nipples and 2 whirls of hair. Sirokha: None. Corrales: None. Kuang: None. Pickl1,4 1MGZ - Medizinisch Genetisches Zentrum, Munich, Germany, 2Pettenkofer School of Public Health, Munich, Germany, 3Institute for Medical Information Processing, Biometry, and Epidemiology –IBE, LMU Munich, Munich, Germany, 4Medizinische Klinik und Poliklinik IV, Campus Innenstadt, Klinikum der Universität München, Munich, Germany, 5Department of General, Visceral and Thorax Surgery, Klinikum Ingolstadt, Ingolstadt, Germany, 6Department of General, Visceral, Vascular and Transplant Surgery, University Hospital Munich, Ludwig-Maximilians University of Munich, Campus Großhadern, Munich, Germany, 7Department of General, Visceral, Thoracic and Endocrine Surgery, Klinikum Garmisch-Partenkirchen, Teaching Hospital, Ludwig Maximilian University Munich, Garmisch-Partenkirchen, Germany, 8Department of Hematology and Oncology, Vivantes Klinikum Neukoelln, Berlin, Germany, 9Department of Oncology, Vivantes Auguste-Viktoria-Klinikum, Berlin, Germany, 10Department of Oncology and Hematology, Barmherzige Brüder, Klinikum St. Elisabeth, Straubing, Germany. Our study suggests that ddPCR can also be an effective and sensitive method for the detection of the T315I mutation in the setting of CML. M.A. Ramos-Arroyo: None. Belghith: None. Our results emphasize the necessity of functional analysis of new variants in these regions with the objective of determining their biological effect and possible influence on FH phenotype, allowing the correct diagnosis of the disease. Materials and Methods: We investigated 357 PD patients from Republic of Bashkortostan. P01.079.C The contribution of chromosomal abnormalities in the formation of sporadic and recurrent early reproductive losses Iryna Tkach 1, Nataliya Huleyuk1, Danuta Zastavna1, Thomas Liehr2, Ewa Ciszkowicz3 1Institute of Hereditary Pathology, NAMS of Ukraine, Lviv, Ukraine, 2Jena University Hospital, Friedrich Schiller University, Institute of Human Genetics, Jena, Germany, 3Department of Biotechnology and Bioinformatics, Faculty of Chemistry, Rzeszow University of Technology, Rzeszow, Poland. Conclusions: The spectrum of F9 variants identified in the Portuguese population significantly overlaps that observed in other populations. McMullan: None. The most frequent mutations were: p.H1047R in 42% of the cases and p.E545K in 22%. Panthan: A. Results: The AVENIO Edge Quant kit results and sequencing metrics were similar between automated and manually prepared samples for all representative panels. Enattah Biotechnology Research Centre, Tripoli, Libyan Arab Jamahiriya. Results: Of the 19,189 CMA tests were performed in our laboratory, 107 STRC microdeletions were found (0.56%), followed in frequency by OTOA deletions (39, 0.2%), and DFNB1 locus deletions (10, 0.05%). Results: No pathogenic variants in Hennekam syndrome-associated genes (CD55, FAT4, CCBE1 and ADAMTS3) have been found. Cerezo: None. Vajda: None. All patients (n = 5) with poor or ultra-metabolisers status presented adverse drug reactions in relation with opioid therapy. Pendina 1, Andrei V. Kagami: None. City of Hope Comprehensive Cancer Center, Monrovia, CA, USA, 11Clinical Cancer Unit. Results: Similar to2 we observed that the strongest genetic associations lie in the regions containing genes from the core pathway; that genetic variation near the core pathway genes explains minor proportion of heritability; that periphery is enriched for genes with tissue-specific expression. This research was supported by the EU project 2014-2020.4.01.15-0012, and Estonian Research Council PUT736, PUT PRG555 grants. This work was supported by the Systems Biology Fellowship to Y.A.B., Presidential Fellowship (grant no. Wahl: None. Al-Kasbi: None. We provide the TR profile for comparison with other populations as well as for the use in diagnostics of rare genetic disorders as a source of background structural genetic variability. We used genome-wide association studies (GWAS) data to impute HLA types and to performed multiple statistical analyzes, to examine the association of specific HLA types, haplotypes and amino acid changes with PD. The segregation analysis excluded the possibility of germline mosaicism as proband's three sons are negative for the maternal TP53 mutation. A number of genes have been associated with rare autosomal dominant and severe sporadic forms of epilepsy; however, the underlying cause of epilepsy remains unknown in the majority of cases. Clayton: None. Sanger sequencing was used to segregate the candidate variant in available family members, and analysis of cDNA allowed characterization of the mutant transcript. Jupyter notebooks distributed by a JupyterHub were chosen to address these limitations. It is predominantly characterized by early-onset severe periodontitis with premature tooth loss, pretibial hyperpigmentation and skin fragility. We identified two novel frameshift variants, c.1671_1686del:p.(Tyr558Alafs*105) in Patient 1 and c.1716-1722del:p.(Ser573Alafs*93) in Patient 2, and one novel in-frame deletion, c.1861_1884del:p.(Pro621_Ala628del) in Patient 3. In contrast, 253 terms corresponded to a single entity. RNA was obtained from urinary stem cells from the two patients. Thus, we have designed an On-Demand gene panel, including 35 genes associated with HBOC to improve our clinical diagnostic routine, especially in those families that gathers several cancer types, which do not fit into a specific inherited cancer syndrome. Serum erythropoietin was measured by ELISA. But today we remain faced with problems of interpreting the pathogenicity of large CNVs over 3Mb inherited from normal parents, sometimes in a clinical emergency. Ambiguous LOXL1 variant is mostly considered as having negative effect on the development of XFS and glaucoma. Joint fine-mapping that leverages information between related quantitative traits could improve accuracy and precision over single-trait fine-mapping. S.D. Frederiksen: None. Results: There were no differences in IQ between men (34) and women (101). van Golde, Christine E. The presence of BRCA1 (rs80357906, rs80357711) or BRCA2 (rs80359550) variants increases the risk of BC/OC statistically significantly (1,5; HSP90B1 and PCNT) and 8 infra-expressed genes (FCA/p.Cys461Tyr in the GRINB2 gene changes evolutionary conserved amino acid in the ligand-binding domain of the NMDA receptor. At the age of 4y11m, she had febrile seizures and started taking antiepileptic therapy. Najarzadeh Torbati: None. Loizidou1,2, Eleni Kakouri3, Yiola Marcou3, Kyriacos Kyriacou1,2, Andreas Hadjisavvas1,2, Kyriaki Michailidou2,4 1Department of Electron Microscopy/Molecular Pathology, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus, 2The Cyprus School of Molecular Medicine, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus, 3Bank of Cyprus Oncology Center, Nicosia, Cyprus, 4Biostatistics Unit, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus. Liver organoids are an interesting model to develop a gene edition CRISPR/Cas9 strategy as a gene therapy to treat AATD. P06.058.C VARS2-linked mitochondrial disease - an emerging phenotypic spectrum Raquel Gouveia, Márcia Rodrigues, Oana Moldovan, Ana Berta Sousa Serviço de Genética Médica, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisboa, Portugal. Ferrer-Avargues: None. Gabbi: None. P12.083.C The transcription factors TFEB and TFE3 promote tumor growth in Birt-Hogg-Dube' syndrome CHIARA DI MALTA 1,2, Angela Zampelli1, Letizia Granieri3, Luisa Lanfrancone3, Andrea Ballabio1,2,4 1Telethon Institute of Genetics and Medicine (TIGEM), Pozzuoli (NA), Italy, 2Medical Genetics Unit, Department of Medical and Translational Science, Federico II University, Naples, Italy, 3European Institute of Oncology (IEO), Milan, Italy, 4Department of Molecular and Human Genetics, Baylor College of Medicine., Houston, TX, USA. The expression fold change heatmap revealed three clusters with distinct expression patterns in patients. FISH analysis showed that PAFAH1B1 was disturbed by the breakpoints of this structural variant. Segregation analysis and confirmation of NGS data was performed with Sanger sequencing. Results: The molecular diagnostic rate of this targeted NGS panel of 66 genes was 62% (54 of 87 cases). Pirags: None. Marton: None. Results: The first approach (i) was effective in slightly increasing mitochondrial protein expression and respiration in the wild type and intermediate-mutation load cybrids and fibroblasts, but were ineffective in high-mutation load cell lines. A practical limitation of TWAS is the emphasis on cis-eQTL effects on expression due to limited sample sizes of eQTL datasets, which restricts discovery power for trait-related genes whose expression may be influenced by aggregate trans-acting effects. His childhood X-rays showed shortness of long bones and hands' phalanges and typical notches of II and V metacarpus. We report 10 month old deceased boy who initially presented with microcephaly and dismorphic features. Zhvania Pediatric Academic Clinic, Tbilisi State Medical University, Tbilisi, Georgia, 3Centogene GmbH, Rostock, Germany, 4G.Zhvania Pediatric Academic Clinic, Tbilisi State Medical University, Tbilisi, Georgia, 5Bakhutashvili Institute of Medical Biotechnology, Tbilisi State Medical University, Tbilisi, Georgia, 6University Rostock, Medical Faculty, Rostock, Germany, 7Arcensus GmbH, Rostock, Germany. C.A.L. Ruivenkamp: None. Molecular diagnosis enables proper genetic counseling and medical prognosis to patients. Purpose: To examine the implications of reporting heterozygous losses of recessive genes in Chromosomal Microarray Analysis (CMA), based on the incidence of microdeletions of three common hearing impairment genes in the local cohort and the prevalence of sequence variants in these genes in worldwide databases. Bonfanti: None. Gawlik: None. Introduction: Hypertrophic Cardiomyopathy (HCM; MIM #192600) and Heterozygous Familial Hypercholesterolemia (HeFH; MIM #144010) are the most common genetic cardiovascular disorders. The FISH analysis to t(14;18) was negative. Their characterization was done by karyotyping, FISH analysis, array-based comparative genomic hybridization and microarray expression profiling. In both cases, the deletions were inherited from healthy mothers, so these alterations could have incomplete penetrance and high phenotypic variability. Caramizaru: None. Introduction: Osteochondroma represents the most common benign osseous tumour, 20-50%; in familiar occurrence two AD diseases are probable: hereditary multiple osteochondromas (HMO)(ORPHA:321) associated with variants in EXT1(MIM,#133700) or EXT2(MIM,#133701) genes and metachondromatosis (MC)(ORPHA:2499), caused in PTPN11(MIM,#156250). Results: Timing of diagnosis was 1y/o, 2y/o, 3y/o, 4y/o, 9y/o respectively. P17.044.C Digging exome sequencing data: An example of a homozygous mobile element insertion detected in a rare disease cohort Philippine Garret 1,2, Martin Chevarin1,3, Antonio Vitobello1,3, Simon Verdez1,3, Cyril Fournier4,5, Alain Verloes6,7, Emilie Tisserant1,3, Pierre Vabres1,8,9, Orlane Prevel1,9, Christophe Philippe1,3, Anne-Sophie Denommé-Pichon1,3,10, Ange-Line Bruel1,3, Frédéric Tran Mau-them1,3,11, Hana Safraou1,3,10, Aïcha Boughalem2, Jean-Marc Costa2, Detlef Trost2, Laurence Faivre1,10, Christel Thauvin-Robinet1,3,11, Yannis Duffourd1,3 1UMR1231 GAD, Inserm, 21070 Dijon, France, 2Laboratoire Cerba, Saint-Ouen l'Aumône, France, 3Unité Fonctionnelle Innovation en Diagnostic génomique des maladies rares – FHU-TRANSLAD – Dijon University Hospital, Dijon, France, 4University of Burgundy-iSITE – INSERM UMR 1231 – Faculty of Medicine, 21000 Dijon, France, 5Unit for innovation in genetics and epigenetic in oncology – Dijon University Hospital, Dijon, France, 6UMR1141 INSERM – Université Paris Diderot, Paris, France, 7Genetics Department – AP-HP, Robert-Debré University Hospital, Paris, France, 8Centre de Référence maladies rares « maladies dermatologiques en mosaïque » – service de dermatologie – FHU-TRANSLAD – Dijon University Hospital, Dijon, France, 9Service Dermatologie – Dijon University Hospital, Dijon, France, 10Centre de Référence maladies rares « Anomalies du développement et syndromes malformatifs » – centre de génétique – FHU-TRANSLAD – Dijon University Hospital, Dijon, France, 11Centre de Référence maladies rares « déficiences intellectuelles de cause rare » – centre de génétique – FHU-TRANSLAD – Dijon University Hospital, Dijon, France. Material and methods:to answer these questions we have collected among our networks (ACLF and Achropuces) the data of large CNVs without phenotypic consequences in order to map these changes and make a bioinformatic analysis of their characteristics. L.H. Franke: None. Rodriguez-Girondo: None. Employment (full or part-time); Significant; Pacific Biosciences. The results were validated by Sanger direct sequencing. Several additional abnormalities of unknown clinical significance are identified by OGM; 3. This relatively high frequency suggests that CANVAS may represent a considerable fraction of late-onset ataxias. The additional explanations were estimated as short (up to 5 minutes) in 36.9% of the cases, intermediate (5 to 15 minutes) in 59.9%, and long (over 15 minutes) in 2.6% of cases. At the same time, T21 prevalence among live born decreased from 9,41 to 6,65 and the proportion of eliminated fetuses with T21 increased from 48,57% to 71,51%, which indicates the sufficient effectiveness of prenatal diagnosis. Trachoo: A. Dianne Keen-Kim Natera, Inc, San Carlos, CA, USA. Soares1,2, Abigail Fraser1,2, Laura D. A.J. Gortan: None. D.P. Pereira: None. Some overgrowth syndromes are associated with an increased risk of Wilms' tumour (WT) warranting screening. Mijovic: None. P22.008.C Genetic counseling during COVID19 pandemic. Our aim was to extend current genetic testing of patients with idiopathic erythrocytosis and to discover new disease-driven pathways and genes. There were no significant associations between carrier-status and phenotype scores for other genes, or in primary-care subgroup analyses. OR markers were higher in women with PCOS. Lidereau: None. Research is part of the project FSRG-2020-0014 "Arctic Genomics: epidemiology, heredity and pathology". We performed a clinical exome sequencing (CES) analysis at birth. Conclusions: TFAP2B haploinsufficiency likely underlies CIPO pathogenesis, as this gene seems to be required for intestinal development and function. Additionally, the high diagnostic yield seen in prenatal cases is valuable information for genetic counseling regarding natural history and prognosis. Patient 2 was also a female, aged 79, who had more than 50 colorectal adenomas removed on three colonoscopies in less than 2 years. Anan: None. Uusimaa* contributed equally: None. Guigo: None. These type of mutations form new or enhance the effect of acceptor or donor splice sites, leading to the inclusion of non-coding exons in the template RNA and affecting protein function. Broutin: A. These SDs are susceptibility factors for recurrent chromosomal rearrangements mediated by non-allelic homologous recombination (NAHR). Rusch: None. Conclusions: Six new associations were identified, interpopulation differences in allele frequencies were determined. Variant prioritization by HADA helped to reach a fast and precise identification of the underlying causes. Koroleva: None. Rohlin: None. Results: The SPOP C203Y and S236R pathogenicities were 93% and 90%, respectively. Duquenne: None. P06.028.A Pancreatic expression of genes connected to glucose metabolism - nutrigenetic regulation Ivelina Mihaleva, Margarita Strokova, Eliana Dimova, Pavlina Gateva, Ivanka Dimova Medical University of Sofia, Sofia, Bulgaria. Marenne: None. Results: We examined a total of 3,627 exonic SNPs in the DMD gene. This work provided evidence this Alu insertion is linked to the proband's phenotype. The registry is built on MOLGENIS open-source software, providing flexible rich data structures, user friendly data import and querying, and FAIR interfaces for programmatic data exchange. Here, we describe a very early-onset neurodegenerative syndrome caused by loss-of-function mutations in the multiple inositol polyphosphate phosphatase 1 gene (MINPP1). Materials and Methods: The study group included 43 female football players older than 13 years and actively training football more than 4 years. We have compared the change in diversity post versus pre intervention (T2-T1), in the intervention relative to the control group. Bone marrow failure, pulmonary disease and predisposition to malignancy are the primary causes of mortality. Although these conditions exhibit variable expressivity, incomplete penetrance and clinical overlap, some genotype-phenotype correlations have been described. Stegel: None. Wissely: None. Conclusions: A complex structural variant (SV) involving exon 12 of GSN causes a novel form of potentially lethal 'cutaneous-internal organ amyloidosis' that is clinically, genetically and mechanistically distinct from Finnish-type amyloidosis. Escámez: None. Results: Contrary to wt SOX4, which was able to induce ectopic luciferase expression when co-expressed with POU3F2, this effect was abolished for both pathogenic SOX4 variants (Arg61Gln and Glu27*). Most of the analyzed transcripts corresponded to protein coding regions of the human genome (13683). Jain: None. The mitochondrial respiratory chain (MRC) complex III (CIII) associates with complexes I and IV (CI and CIV) into supercomplexes. Acknowledgements. Ownership Interest (stock, stock options, patent or other intellectual property); Significant; Invitae corp. S.G. Kyurkchiyan: None. Cogulu: None. Biochemical profiles showed marginally elevated levels of lipids in four patients, p-LDL cholesterol: 3.8-4.4 mmol/L (ref: A p.Gly977Arg N26 RNF135 NM_032322.4 5 rs61749868 c.1245G>T p.Trp415Cys N27 GAB2 NM_012296.3 4 rs561641037 c.862A>T p.Ile288Phe N27 RASAL1 NM_001193521.1 16 rs142556970 c.1804T>C p.Phe602Leu N28 PHF12 NM_001033561.2 8 - c.1246C>G* p.His416Asp N43 RAF1 NM_002880.3 17 - c.1811C>G p.Ser604Cys N75 RASAL2 NM_004841.4 6 - c.898C>G* p.Gln300Glu N75 RASA1 NM_002890.3 20 - c.2656C>T p.Pro886Ser N76 SARM1 NM_015077.4 9 rs144613221 c.1498T>C p.Tyr500His N80 LRP1 NM_002332.3 51 rs962402779 c.8218G>A p.Glu2740Lys N80 PAK4 NM_001014834.3 3 - c.449A>G* p.Gln150Arg N82 RASAL3 NM_022904.3 13 - c.1983G>A* p.Met661Ile N83 GAB2 NM_012296.3 3 rs770269898 c.350A>G p.Glu117Gly *Novel variants, not reported in any of the consulted databases P. Regier: None. As several gene-targeted therapies for PD have now reached the clinical trial stage (not yet the case for PRKN-related entity), the clinical utility of genetic testing for PD has expanded considerably. P10.025.A Bionano optical genome mapping and southern blot analysis for FSHD detectionJeroen Depreeuw, Barbara Dewaele, Sascha Vermeer, Gert Matthijs, Valérie Race Center for Human Genetics, University Hospital of Leuven, Leuven, Belgium. Materials and Methods: We analysed 88 subjects from 19 families: 66 disease-variant carriers and 22 unaffected. Intragenic deletion/point mutations in ZC4H2 gene have been identified responsible for this X-linked condition (OMIM 314580/ZARD: 'ZC4H2 associated rare diseases'). Rare disease diagnosis is a key priority of the UK Rare Disease Framework. Patients suffered from motor-greater-than-sensory polyneuropathy with an age of onset mostly within the first decade of life. Chavez Chavez: None. We used MMSE, the Beck depression inventory (BDI) and the state-trait anxiety inventory (STAI). There are few case reports suggesting the importance of this enzyme complex malfunction as triggers for lactic acidemia with elevated serum lactate levels. Rothhammer: None. Csutak: None. As a manipulation check of our intervention, we quantified the abundance of the administered beneficial bacteria Lactobacillus and Bifidobacterium, as it is expected to show increased abundance post vs. M.L. Paynton: None. Grozescu: None. Results: The diagnostic yield of this targeted reanalysis was 24.4%, with a definite diagnosis identified for 73 of the 299 patients. CD4+ T cells have been highlighted as the most relevant cell type to RA pathogenesis by non-coding RA-risk variants on CD4+-specific regulatory elements. For our type 2 diabetes DNA methylation discovery study cell-free saliva was collected from a diabetic patient cohort (type 2 diabetes, pre-diabetes, gestational diabetes, healthy) and extracellular vesicles thereof prepared. Intriguingly, a member of one of the families had a high-grade serous ovarian cancer (malignant neoplasia not usually associated with Li-Fraumeni Syndrome) at 23 years of age. coli, K. We observed no difference between the phenotype of probands with de novo and inherited CHD3 variants, including developmental delay/intellectual disability (100%), speech delay (100%) and facial dysmorphisms. Zech: None. Marconi: None. Population studies demonstrate significant case stratification by PRS for breast cancer, coronary artery disease, major depression, osteoarthritis and age-related macular degeneration. Though legal recognition occurs at the provincial rather than federal level in Canada, we advocate for a pan-Canadian approach to develop strategies and resources to further provincial and territorial pursuit of legal recognition. ERCC2: c.2164C> T mutation was previously reported as compound heterozygous with pathogenic p. Atlan: A. Despite diagnostic advances, ~50% of patients remain undiagnosed. BEEC affects 1 in 10,000 births, with a twofold higher incidence in males. Hastie: None. Introduction: FIP1L1-PDGFRA fusion, which originates from an interstitial deletion in 4q12, is observed in diverse eosinophilia-associated hematologic disorders. K.J. van der Velde: None. Samples were hybridized to Clarium-S human array and scanned using GeneChip System of Affymetrix. Andrusaityte: None. Cytogenetic analysis of uterine leiomyoma (UL) cell cultures reveals clonal chromosome abnormalities in 60% of ULs. The latter are believed to occur secondarily during tumorigenesis. Béliard: None. The information on grants: the "National Natural Science Foundation of China" (No.81800780) X. Conclusions: NGS gene panel CZECANCA proved to be a valuable tool that brought improvement in diagnostic yield of FAP patients in our cohort. control fibroblasts. Zeke: None. Results: Because of muscular hypotonia SMA was excluded. We report a 45-year-old woman with an ileocecal adenocarcinoma showing MSI and loss of MLH1 and PMS2 by IHC. F.F. Aljedaemi: None. Thanks to a short turn-around time, an affordable price and a great robustness, this method has been widely adopted by clinicians nationwide for dominant paternally-inherited disorders, or as a first test for recessive disorders. Employment (full or part-time); Modest; Thermo Fisher Scientific Baltics UAB. Cases of isolated polysyndactyly were attributed to mutations in the third third of GLI3. Díez Obrero: None. Eltigani: None. Preliminary data from the TeleNEwCARe project show that remote counselling meets the approval of patients, allowing a confidential relationship with clinicians and an effective sharing of information. Funding This project was funded through grants from the National Oncology Care Support Program (PRONON (25000.056766/2015-64)) from the Ministry of Health and from donations from Cotemig group. P13.012.A Two novel deletions in the 5 Untranslated region of GNAS gene as a cause of pseudohypoparathyroidism type 1A Louise-May Thibaut 1, Arnaud Molin1, Christine Francannet2, Benjamin Dauriat3, Andreea Apetrei1, Nicolas Richard1 1Normandy University Hospital, Caen, France, 2Clermont-Ferrand University Hospital, Clermont-Ferrand, France, 3Limoges University Hospital, Limoges, France. Conclusions: The high sensitivity of this method is compatible with its use for plasma circulating tumor DNA (ctDNA) analysis for early tumor detection in DICER1 syndrome patients. The in vitro kinetic analyses indicated that individuals with the S156C199 haplotype might have a decreased ability to metabolise benzoate when compared to individuals with the S156 haplotype. The two patients with isolated dystonia carried one missense variant of unknown clinical significance (p.Arg1762His) or one splice-site variant (c.5198-4_5206del). AlShehri: None. Regulatory activity of putative CREs was tested using in vitro luciferase assays. PRKN analysis was performed by Sanger sequencing and/or MLPA, or a NGS multigene panel. More over, there was a pulmonary nodule at the apical segment of the right lung. BRPF1 gene on 3p26-p25 encodes a protein involved in epigenetic regulation, through interaction with histone H3 lysine acetyltransferase KAT6A and KAT6B of the MYST family. Alembik: None. Introduction: Hypermobile Ehlers-Danlos syndrome (hEDS) is a non-inflammatory connective tissue disorder. Our results indicate that genetic predisposition to higher fetal and not maternal insulin resistance is associated with birth weight. It is characterized by cochlear incomplete partition with fistulous communication with internal auditory canal. Imbalance between short and full-length LEF1 isoforms may lead to cell survival in ALL. Although the mechanisms of disease of C9ALS/FTD remain unknown, a gain of function of a toxic mRNA and RAN-translation have been proposed as triggering pathological mechanisms. ConclusionThe use of WES in foetuses with ultrasound defects previous an accurate compilation of family history is required to determine the pathogenicity of the variant and specific risk of recurrence. P18.033.C Enrollment engagement strategies for a preemptive genomic screen Michelle Marie Moore, Alexander van Gerrevink, Bethany Tucker, Murat Sincan, Catherine Hajek Sanford Health, Sioux Falls, SD, USA. Conclusion: Especially MLH1- and MSH2-deficient tumors without MLH1-promoter methylation are often not due to Lynch syndrome, but have two somatic MMR aberrations. P03.033.A Clinical description of a new type of mucopolysaccharidosis in Yakutia Saina Novgorodova 1, Aytalina Sukhomyasova1, Elizabeth Gurinova2, Vera Argunova2, Lena Nikolaeva3, Nadezhda Maximova1 1Research Laboratory "Molecular Medicine and Human Genetics" of the Medical Institute NEFU, Yakutsk, Russian Federation, 2Republican hospital №1-National Center of Medicine, Yakutsk, Russian Federation, 3Republican Hospital No. 1-National Center of Medicine, Yakutsk, Russian Federation. Rodríguez-Pérez: None. The impact of the pandemic on Healthcare Professionals is clear; decreased patient and colleague contact is proving challenging. Conclusion: CNVs constitute a complex subgroup in placental mosaicism. Polat: None. Results: 137 patients were studied. The following variants were found either in homozygous or in compound heterozygous state and co-segregated in these families: c.530G>A;p.(Arg177Gln), c.934C>T;p.(Arg312Trp), c.881G>T;p.(Arg294Leu), c.1702C>T;p.(Arg568Trp). The study was funded by Engels Family Fund and FY2020 Tuberous Sclerosis Alliance Postdoctoral Fellowship Award (KK) K. P25.016.C Genetic predisposition to severe COVID-19 symptoms differs by sex within the ALFA studyNatalia Vilor-Tejedor1,2,3, Patricia Genius 1,4, Blanca Rodríguez-Fernández1, Carolina Minguillon1,5,6, Karine Fauria1,5, Manuel Castro de Moura7, David Piñeyro7, Manel Esteller7,8,9, Jose Luis Molinuevo1, Roderic Guigo2,10, Arcadi Navarro1,9,11, Eider M. D.C.Q. Soares: None. Exome sequencing revealed a homozygous missense mutation c.866A>G, (p.Tyr289Cys) in the NARS1 gene. TGCA can provide a genome-wide atlas for the overall genetic contributions in each particular domain of human complex traits. Genotyping of the rs4054823 C/T polymorphism, located on the chromosome 17p12, was performed by allelic discrimination with Taqman 5'-nuclease assays. The MDC score predicted the underlying mitochondriopathy-associated genotype with a sensitivity of 0.59 (0.41-0.75) and a specificity of 0.99 (0.96-1.00). E.M. Borkowska: None. Karamisheva: None. Actual data indicate a high heterogeneity of variants in F9. Rezapova: None. Sadovnychenko 1,2, Halyna V. Lepisto14, Marta Puzzono6, Ingrid Winship15, Veronica Zuber6, Gabriela Möslein16 1University Medical Center Rotterdam, Rotterdam, Netherlands, 2Erasmus MC Cancer Institute, Rotterdam, Netherlands, 3University Hospital Bonn, Bonn, Germany, 4University of Bonn, Bonn, Germany, 5Tampere University Hospital, Tampere, Finland, 6University IRCCS San Raffaele Scientific Institute, Milan, Italy, 7Manchester Academic Health Science Centre, Manchester, United Kingdom, 8, St Mary's Hospital, Manchester, United Kingdom, 9University Hospital of Copenhagen, Copenhagen, Denmark, 10Imperial College London, London, United Kingdom, 11St. Marks Hospital, London, United Kingdom, 12Netherlands Cancer Institute, Amsterdam, Netherlands, 13Leiden University Medical Center, Leiden, Netherlands, 14University Hospital of Helsinki, Helsinki, Finland, 15University of Melbourne, Melbourne, Australia, 16, Academic Hospital University of Düsseldorf, Duisburg, Germany. The classical symptoms of MFS include skeletal, cardiovascular and eye abnormalities. Inter- and intra-familial variability were observed; the visual acuity ranged from 0.0 to 1.6 LogMAR and fundoscopic findings ranged from visually insignificant, confluent, drusen-like macular deposits to coloboma-like macular lesions. Severgnini: None. Yun: None. Correa-Vela: None. Conclusion: The results support the use of CMA as first-tier test for syndromic microcephaly, especially for severe microcephaly presented with skeletal and/or cardiovascular anomalies. Demir: None. Hence, we identified 5 novel fusions in pediatric leukemia patients: DNAJC1-KMT2A, FTH1-KMT2A, MLLT10-ANGPT1, MLLT10-AP001107.9, MLLT10-MKX and TBL1XR1-EAF2. Ozkan: None. A small proportion of consumers are left dissatisfied, have negative experiences or are adversely impacted. Castellvi-Bel: None. J.A. Tenorio: None. Results: A homozygous variant was identified in all nine cases and eight of them were novel. We recently reported 28 patients with a neurodevelopmental disorder (NDD) harboring de novo amino acid changes in AGO1 (Schalk, Cousin et al, BioRxiv 2010). Genetic counseling was given to the family of the patient. Valanciute: None. Brett: None. The deduplication process was performed using a combination of Picard, fgbio and bwa tools. The most severe histopathological phenotype in male infertility is the Sertoli cell-only syndrome (SCOS) which is characterized by total germ cell aplasia in testicular tissue. Introduction: Body-mass index (BMI) is a risk factor for complex disease known to be influenced by genes acting via both metabolic pathways and appetite regulation. Houtman: None. S.V. Mullegama: None. We studied a large international cohort of 79 patients harbouring GDF5 variations in order to: 1) Describe precisely the clinical and molecular data of patients; 2) Identify rare phenotypes and 3) Demonstrate genotype-phenotype correlations. Ołdak: None. Genotype rs13041792-A/A was associated with increased levels of fasting blood glucose (FBG) in entire group of T2D patients (P = 0.032) and diabetic males (P = 0.026). Brysse: None. A hypothesis is proposed explaining quantitative f-SatIII and TR polymorphism under stress. Olausson: None. The prognostic impact of ACTB_short was also retained after multivariable analysis (HR: 4.88, 95%CI 1.07 -22.17, P = 0.040). Expression of miR-195-5p was significantly downregulated (p = 0.032) between the SCC and adjacent normal. Tammer: None. Pipiras: None. Sultan: None. Kokitsu-Nakata1, Camila W. Niceta: None. Hypermethylation of the MLH1 promoter was detected in 2 MSI-H patients, and BRAF V600E mutation was detected in 2 MSI-H patients. Lebedev2, Ilgar Z. Developmental delay appeared to precede seizure onset, suggesting SETD1B dysfunction impacts physiological neurodevelopment even in the absence of epileptic activity. Additionally, we introduced MS to the O-glycoform profiling of apoCIII. In 252 of the families (90.0%), a trio WES was performed. Gómez-Andrés: None. Today more than 600 mutations in PAX6 have been reported, about 100 of them were annotated as affecting splicing. Villa: None. P04.081.B Association between a functional polymorphism within the IL-17RC gene and idiopathic scoliosis in Bulgarian population Svetla Nikolova 1, Milka Dikova2, Alexandre Loukanov3 1Sofia University, Sofia, Bulgaria, 2Medical University-Sofia, Sofia, Bulgaria, 3Saitama University, Saitama, Japan. Vaske: None. Ahring36, Rikke S. The contribution of most of these genes to the development of neuroendocrine tumors (NET) is largely unknown. Results and conclusions. Magistrelli: None. Discussion: CMA is the gold standard method for detecting CNVs. As higher resolution scanning chips are used, smaller CNVs can be detected. P11.023.A miRNA-free rare pathogenic CNVs could drive toward variable CAKUT phenotypes Ivan Zivotic, Ivana Kolic, Kristina Popic, Jelena Filipovic Trickovic, Ana Djordjevic, Maja Zivkovic, Aleksandra Stankovic, Ivan Jovanovic "Vinca" Institute of nuclear sciences, Inslitute of the national interest of the Republic of Serbia, University of Belgrade, Belgrade, Serbia. In addition to clinical phenotyping we performed several analyses. Debeljak: None. Tanas: None. Eiengård: None. Speakers Bureau/Honoraria (speakers bureau, symposia, and expert witness); Modest; Novartis, Amgen, Kaneka. Conclusion: This study for the first time ever reports the association of IRAK2 rs3844283, IRAK2 rs708035, and the corresponding haplotypes with RA. Males flies were more affected than females, suggesting gender specific vulnerability. Introduction: PCSK9 is the third gene involved in familial hypercholesterolemia (FH). Krug: None. de Sanjosé: None. Introduction: The CLEC16A (c-type lectin protein 16A) gene locus has frequently been associated with susceptibility to various autoimmune disorders including multiple sclerosis, type - 1 diabetes, rheumatoid arthritis and primary biliary sclerosis. P03.003.C The mild effect of the COL4A5 variant p.Gly624Asp in a group of 15 Polish patients with Alport syndrome Paulina Halat-Wolska 1, Elżbieta Ciara1, Lukasz Obrycki2, Katarzyna Gadomska-Prokop2, Dorota Piekutowska-Abramczuk1, Joanna Kosińska3, Małgorzata Rydzanicz3, Piotr Stawiński3,4, Beata Chałupczyńska1, Kamila Frączak1, Marzena Gawlik1, Dorota Jurkiewicz1, Paweł Kowalski1, Magdalena Pelc1, Dorota Siestrzykowska1, Szymon Szyszkowski1, Dorota Wicher1, Ryszard Grenda2, Krystyna Chrzanowska1, Rafał Płoski3, Mieczysław Litwin2 1Department of Medical Genetics, The Children's Memorial Health Institute, Warsaw, Poland, 2Department of Nephrology, The Children's Memorial Health Institute, Warsaw, Poland, 3Department of Medical Genetics, Warsaw Medical University, Warsaw, Poland, 4Department of Genetics, Institute of Physiology and Pathology of Hearing, Warsaw, Poland. Physical examination revealed dyspnea, low BMI (19.2 kg/m^2), severe bronchial obstruction (FVC 54%, FEV1 33%), bilateral bronchiectasis on CT. Kandaswamy: A. M.B. Muijzer: None. P08.073.C Heterozygous Loss of Function Variants in TBCK Cause a Mild Neurologic Syndrome in Humans and Mice Abdias Diaz-Rosado Children's Hospital of Philadelphia, Philadelphia, PA, USA. P08.041.C Frameshift variant in SETD5 in a patient presenting a KBG syndrome Angela Teresa Abad Perez 1, Felix Boschann1, Birgit Jödicke2, Denise Horn1 1Institute of Medical Genetics and Human Genetics, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany, Berlin, Germany, 2Center for Chronically Sick Children, Department of Paediatric Endocrinology and Diabetes, Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany. Traberg: None. Vasseur: None. Material and methods: Shotgun transcriptome sequencing was performed using RNA extracted from nasopharyngeal swabs of SARS-CoV-2 positive patients. These 6 genes will be tested to evaluate their translational role for a better understanding of the main pathogenetic mechanisms of MS, the identification of new therapies and the design of clinical trials for MS treatments. Materials and Methods: Through GeneMatcher we collected clinical data of 13 patients harboring likely causal variants in KIF4A. NF1 is caused by variants in the neurofibromin (NF1) gene, arising de novo in ~50% of cases. Background: For decades, the inheritance mechanism of genetic disorders was explained through the "one gene-one disease" paradigm. CS is a rare systemic syndrome with a great clinical variability, characterized by coarse facies, hypertrichosis, osteochondroplasia and cardiac anomalies. Januel: None. Tulpakov: None. A.M. Ageez: None. Materials and Methods: In the present work we have studied 2 groups of patients with PD and 2 comparison groups. Castells: None. They are highly heterogeneous and clinical findings are often non-specific, so accurate diagnosis often relies on expert interpretation of radiological findings. Both detected variants were classified as pathogenic or likely pathogenic according to ACMG. Rashbass: None. P04.058.C Exome sequencing combined with RNA sequencing clarifies the mode of inheritance of MYH3-associated spondylocarpotarsal syndrome: a case report Marija Volk, Karin Writzl, Matevž Jus, Aleš Maver, Helena Jaklič, Borut Peterlin Clinical institute of genomic medicine, UMC Ljubljana, Ljubljana, Slovenia. Moskvitin1,2, Aitalina L. Protocols such as hybrid capture can take several days to complete and require multiple manual interactions and pipetting. Warmerdam: None. A 180A_50% 180A_25% 180A_12,5% 180A_6,125% 110M_ unknown TOT (X) 720 656 739 760 673 WT (X) 371 549 661 730 591 MUT (X) 349 107 78 30 82 % 48,47 16,31 10,55 3,95 12,18 A. The RQOC developed two knowledge scales for non-invasive prenatal screening and hereditary cancer testing for MMIC decision tools. The disease can be inherited in an autosomal dominant (AD) or autosomal recessive (AR) manner. One possible explanation is the influence of epigenetic modifications in genes, important for oncogenesis. The rationale of this study was to analyze mutations in frequent genes in a cohort of Russian patients with congenital glaucoma.Twenty-one Russian patients with a primary diagnosis of congenital glaucoma were included in the study. Gadomska-Prokop: None. A.R. Tarelho: None. Byers1,2, Jamie M. Reif: None. This is the first time, a homozygous PTPN2 variant is associated with an early onset CD. Subtype analysis did not yield suggestive results. Results: Statistically significantly lower methylation levels were registered at a CpG site (chr1:94374293, GRCh37 [hg19]) in GCLM in patients with CAD compared with the control group (6,1% [4,8%; 7.6%] (median and interquartile range) versus 14.5% [10.4%; 21,7%], respectively, $p = 1.49 \times 10^{-11}$). Lopez-Laso: None. Torres Cuevas: None. Ocular anterior segment disorders are clinically and genetically heterogenous conditions, by demonstrating the underlying genetic cause we gave appropriate genetic counseling and follow-up. In detail, the following steps have been performed:1. P24.021.D Fine mapping of GWAS loci associated with multiple sclerosis to dissect the pathogenetic role of drug target genes Miriam zuccalà*1, Alessandro Pizzino*1, Nadia Barizzone1, Ferdinando Clarelli2, Chiara Basagni1, Melissa Sorosina2, Elisabetta Mascia2, Domizia Vecchio3, Mattia Pozzato4, Cristoforo Comi3, Roberto Cantello3, Vittorio Martinelli5, Giancarlo Comi6, Maurizio Leone1,7, Massimo filippi5,8, Filippo Martinelli-Boneschi9, Federica Esposito2, Sandra D'Alfonso1 1Department of Health Sciences, University of Eastern Piedmont, Novara, and IRCAD (Interdisciplinary Research Center of Autoimmune Diseases), Novara, Italy, 2Laboratory of Human Genetics of Neurological Disorders, Institute of Experimental Neurology (INSPE), Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan., Milano, Italy, 3MS Centre, SCDU Neurology, AOU Maggiore della Carità, Novara, Italy, Novara, Italy, 4Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurology Unit and Multiple Sclerosis Center, Milan, Italy, Milano, Italy, 5Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Milano, Italy, 6Institute of Experimental Neurology, San Raffaele Scientific Institute, Milan, Milano, Italy, 7Unit of Neurology, Fondazione IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, FG, Italy, Milano, Italy, 8Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan, Milano, Italy, 9Dino Ferrari Centre, Neuroscience Section, Department of Pathophysiology and Transplantation (DEPT), University of Milan, Milano, Italy. S.P. Boudko: None. Antonarakis28, Henry Houlden2, Taroh Kinoshita16, Philippe M. Meshkov: None. These genes are responsible for the regulation of the ubiquitin-ligase complex. LF UK) and University Hospital Motol, Prague, Czech Republic, 2Centre of Molecular Biology and Genetics, University Hospital Brno, Brno, Czech Republic, 3Neurogenetic laboratory, Department of Paediatric Neurology, Second Faculty of Medicine (2. Lanillos: None. More recently it was reported that de Novo and Bi-allelic pathogenic variants in NARS1 Cause neurodevelopmental delay due to toxic gain-of-function and partial loss-of-function effects. Introduction: Coronary artery disease (CAD) is heritable and has a polygenic architecture. P09.107.D A Patient with Parkinsonian-Pyramidal Syndrome due to a TBK1 Mutation Jelena Pozojevic 1, Diego Santos-García2, Teresa de Deus Fonticoba3, Mónica Kurtis4, Josep Gamez5, Christine Klein1, Mariana H. Carmi: F. Here, we describe a MAP Libyan family in who multiple cases were identified as having digestive cancers. van de Beek: None. Results: 126 patients were identified, including one familial WT. Omics technologies provide new perspectives to better understand disease processes. Gardini: None. Naharro: None. Subsequent independent verification by bilingual genetics staff elsewhere has been arranged. Since its creation, the NCG implemented a multilingual clinical genetic service providing genetic consultations for app. Conclusions: This study once more demonstrated saliva to be a most promising sample matrix for disease diagnostics. Talapko: None. Gavrilova, Rinat A. We analyzed the cosegregation of RPL3L variants in the family when relatives were available. Conclusions: Through assessment of allelic mRNA expression and splicing, long-read RNA-seq facilitates variant interpretation and may ultimately increase diagnostic yield. Garifullina: None. Cenani-Lenz (CLS) is an infrequent congenital malformation characterized by syndactyly of the hands with abnormalities of the forearm bones that can be also present in the lower limbs, renal abnormalities and dysmorphism. P06.018.C Novel deletion in PHKA2 gene in glycogen storage disease type IXa Amanda Herranz-Cecilia 1,2, Carmen Rodríguez-Jiménez1,2, Carmen Camarena3, Javier Sanguino1,2, Rocío Rosas Alonso4,5, Ana Carazo1,2, Juan Manuel Montejo-Gadea6, Ángela Del Pozo7,8, Sonia Rodríguez Nóvoa1,2 1Metabolic Disease Laboratory, Genetic Department, Hospital Universitario La Paz, Madrid, Spain, 2Group of "Dislipemias of Genetic origin and Metabolic Diseases", IdiPAZ, Hospital Universitario La Paz, Madrid, Spain, 3Paediatric Hepatology Service, Hospital Universitario La Paz, Madrid, Spain, 4Pharmacogenetic Unit, Genetic Department, Hospital Universitario La Paz, Madrid, Spain, 5Experimental Therapies and novel biomarkers in cancer, Instituto de Investigación Sanitaria del Hospital La Paz (IdiPAZ), Madrid, Spain, 6Preanalytic Section. Lebedev: None. Introduction: The mostly known fibrillinopathy, Marfan syndrome (MFS), is a multisystem disease with a unique combination of skeletal, cardiovascular and ocular features. Karathanasis: None. Insodaite: None. Ninety five samples from psoriasis patients' group and 77 samples from a control group of healthy people were examined. Our results suggest that XIST on the future active X is repressed in both sexes just before, or at the time that, the pluripotent factors are upregulated during the 4-8 cell stage in the human and bovine embryo, well before the late blastocyst when XIST is upregulated on the inactive X in females. Proportionate short stature is a common condition (3% of general population) with a heterogeneous genetic etiology. P04.088.A What are key parameters for obtaining the most likely clinical diagnosis from the wide phenotypic spectrum of skeletal dysplasia in patients with previously identified disease-causing gene variant Marija Mijovic 1, Bojan Bukva2,3, Jelena Ruml Stojanovic1, Aleksandra Miletic1, Brankica Bosankic1, Hristina Petrovic1, Goran Cuturilo1,3 1University Children's Hospital, Department of Clinical Genetics, Belgrade, Serbia, 2University Children's Hospital, Department of Orthopedic Surgery, Belgrade, Serbia, 3Faculty of Medicine, University of Belgrade, Belgrade, Serbia. We present a 5 years old patient with typical 3MC phenotypic characteristics, including blepharophimosis, telecanthus, high arched eyebrows, fifth finger clinodactyly and horseshoe kidneys. Goh: None. Pathway analysis identified IRAK1 and TRAF6 as miR-146a target genes. In silico, this altered donor site probably affects mRNA splicing. Merkler: None. Vos1, Winette T. Aim of present study was to establish the crucial clinical and/or genetic parameters for obtaining the diagnosis in three patients with previously unclassified skeletal dysplasia in whom the causal gene variant was identified. H.M.W. Verheul: None. Results: Whole-genome sequencing (WGS) revealed a missense variant c.28G>A (p.Val10Met) in the ACTG2 gene in the mother and the sons, and deletion of ACTG2 exon 1 (non-coding) in the sons and presumably in the father. Employment (full or part-time); Significant; OneOme. Thus, we are able to provide an attractive perspective for the feasibility of carrier status screening, possible genetic counselling at the base for prevention and early treatment strategies of this hereditary syndrome. Syx: None. Conclusion: To date none of the above-mentioned combination of alleles detected in the siblings and the mother are described in the cftr2.org database. Ng1, Wilfred H. A successful PGT test could be developed for 78 couples with 71 different variants in the NF1 gene. Nikolov: None. Three combined BAP1-inactivation with BRAF V600E, identified alone in the fourth (compound) naevus, whereas the fifth (intradermal) naevus harbored NRAS Q61K. Moreover, the associations remained significant under dominant (Pa = 0.018; ORa = 0.405; 95%CI = 0.192-0.854), over-dominant (Pa = 0.002; ORa = 0.271; 95%CI = 0.117-0.627) and additive (Pa = 0.003; ORa = 0.279; 95%CI = 0.12-0.652) models after the adjustment for age, sex, BMI, smoking, and the presence of arterial hypertension. Generally, patients have severe symptoms of the disease. In addition, the true impact of ES is evident from the opportunity to end patient's diagnosis anxiety, offer family prognosis or timely diagnosis and family planning, proper care protocols, and psychological and emotional well-being. O.S. Aydos: None. Conclusion: Results indicate increased Lp(a) levels as a cumulative effect of multiple variants. We suggest that this diagnostic pipeline might facilitate the identification of undetected genetic variations. Swertz, Birgit Sikkema-Raddatz, Marielle E. N.L. Medvedieva: None. The diagnosis of bilateral osteochondritis dissecans (OCD) was made at the age of 22. Pérez-Jurado: A. Employment (full or part-time); Significant; Phenosystems SA. Alavanda: None. One patient has inherited the variant from her mother and grandmother, neither of whom developed SMARCA4-related cancers. We next analyzed expression profiles of FYCO1 across all 466 compounds tested. The aim of this work is to report the case of our patient and his family with a highly variable phenotype and to review the literature of patients in order to update the spectrum of this rare disease. Earlier, two other deletions in the same area (~8 kb and ~200 kb of size) were identified in Europe. Garret: None. Filatova: None. WDR45 encodes WD repeat domain 45 and has a main role in autophagy, which is a highly conserved and essential cellular homeostatic process. Boter: None. Urreizti: None. Introduction: Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant condition characterized by mucocutaneous pigmentation and PJS hamartomatous polyps. This includes the development and validation of APC-specific adaptations of the generic ACMG/AMP interpretation guidelines (separate abstract), which will improve in particular the classification of the high amount of sequence variants with unknown clinical significance (VUS) in public uncurated resources such as ClinVar. The added benefit of including correlated information largely depends on the number of observations, type of trait and degree of pleiotropy. P12.114.B Liquid biopsy in lung cancer patients shows advantages compared to FFPE tissue mutational analysis Madli Tamm 1, Tarmo Annilo1, Kersti Oselin2, Mart Kals1,3, Katrin Keerma1,4, Paula Ann Kivistik1, Miriam Nurm1,5, Margot Saare1,6, Jana Jaal7,8, Neeme Tõnisson1,9 1Estonian Genome Centre, Institute of Genomics, University of Tartu, Tartu, Estonia, 2Department of Chemotherapy, Clinic of Oncology and Haematology, North Estonia Medical Centre, Tallinn, Estonia, 3Institute for Molecular Medicine Finland, FIMM, HiLIFE, University of Helsinki, Helsinki, Finland, 4Tartu University Hospital, Tartu, Estonia, 5Institute of Technology, University of Tartu, Tartu, Estonia, 6Central laboratory, Diagnostic Clinic, East Tallinn Central Hospital, Tallinn, Estonia, 7Haematology and Oncology Clinic, Tartu University Hospital, Tartu, Estonia, 8Institute of Clinical Medicine, University of Tartu, Tartu, Estonia, 9Department of Genetics, United Laboratories, Tartu University Hospital, Tartu, Estonia. Sleight: None. Bermúdez-de León: None. Gualandi: None. Conclusions: Increasing aCGH resolution to single exons led to detection of small CNVs in known disease genes, some intragenic CNVs can easily be missed using a lower resolution array. Here, we aim to assess the exon 53 PMO-induced skipping in primary cell cultures from these patients.Fibroblasts, from patients enrolled in Study 4053-101, underwent Myo-D induced differentiation and were treated with golodirsen. Materials and Methods: Clinical exome sequencing was performed identifying a de novo heterozygous variant in NIPA1 (NM_144599.5 c.249C>G; p.Asn83Lys). CAPUTO3, Virginie VERKARRE4,5, Fanny REINHART4, Séverine ADAMS1, Christine MAUGARD6, Olivier CARON7, Marine GUILLAUD-BATAILLE1, Pascaline BERTHET8,5, Yves-Jean J. Homozygous c.911dupC (Glu305ArgfsTer21) mutation in the CEP41 gene was found. Poceviciene: None. Truty: None. Bortolini: None. Usually in such context, only the familial variant would be tested. de Die Maastricht University Medical Center, Maastricht, Netherlands. Yunakova: None. P11.030.D Vascular, skeletal and endocrine anomalies in mosaic variegated aneuploidy syndrome 2 caused by biallelic variants in CEP57 María Palomares-Bralo 1,2,3, Marta Pacio-Míguez1, Anna María Cueto-González4,5,6, Sixto García-Miñaúr1,2,3, Ángela del Pozo1,2, Juan José Menéndez Suso7, Francisco J. Interestingly, this attitude was never justified by any evidence, and it is imperative to understand, that all available techniques to study the human genome - at different levels of resolutions, and at level of the single cell or by approaching millions of cells at time - rather complement, than play against each other. A replication was performed in 212 independent patients from the same cohort. Van Steijvoort: None. P05.018.D Mutation burden in patients with small unrepaired atrial septal defects Anne Kathrine Møller Nielsen 1, Camilla Nyboe2, Anne Sif Lund Ovesen2, Sebastian Udholm2, Malthe Mølgård Larsen3, Vibeke Hjprtdal1, Lars Allan Larsen3 1Rigshopitalet, Copenhagen, Denmark, 2Aarhus University Hospital, Aarhus, Denmark, 3University of Copenhagen, Copenhagen, Denmark. zagradišnik: None. Research project parfticipation is in some regions an alternative, however limited, with patients often advised to send samples for examination abroad, or travel themselves for examination outside their country of origin.Huge disparity exists in the approach to genetic testing for IRDs. Greater awareness of genetic testing services is required among the health sector and eyecare professionals. Abasq-Thomas: None. On the multiplicative scale, similar results were obtained for BMI though these did not withstand to Bonferroni correction (Peffect modification: 0.015). Considering the clinical overlapping between skeletal ciliopathies, and the prevalence of EVC/EVC2 gene-dosage anomalies, we recommend a two-tier diagnostic approach integrating a primary search for point mutations by a ciliary targeted NGS analysis, followed by a quantitative assay (MLPA/CMA), waiting for reliable pipelines for the detection of intragenic CNVs throughout NGS technologies.This research was funded by the Italian Ministry of Health, grant numbers RC2019/RC2020 F. Núñez: None. Parents asked for termination of pregnancy. MMR germline variants were present in 2.0% (95% CI 2%-2%, I2=92%), ranging from 1.8% to 7.3% based on completeness of diagnostics and age restriction. Participants were randomised to (1) genetic counselling and standard care or (2) standard care alone (control). Tanaka: None. As a result, scientists are able to study biological systems at a depth never before possible, to find answers to complex biological questions. This will increase report reproducibility and readability for clinicians, ultimately improving patient care. Libraries were prepared from two synthetic RNA control templates and five clinical samples with RT-qPCR Cq values ranging between 18.5 and 30.9. Comparable coverage (depth and uniformity) and 100% concordant SNP calling results were obtained with EDS primers and those obtained from commercial suppliers. Objective: Y chromosome microdeletions are the leading genetic cause of male infertility and their detection is clinically relevant for appropriate genetic counseling. P19.038.B MRE11A locus rs533984 - A marker of selective survival up to the age 85+ in Croatian population eljka Celinćak, Maja etinc, Luka Bočkor, Anita Stojanović Marković, Matea Zajc Petranović, Marijana Peričić Salihović, Tatjana karić-Jurić Institute for Anthropological Research, Zagreb, Croatia. Assouline: None. PDCD1 and AIP showed the highest levels in non recurrent PitNETs, an intermediate level in recurrent PitNETS and lower levels in carcinoma. All together 237 tumors from these patients were tested. Capel: None. However, the extent that sex affects the genetic architecture of ALS is currently understudied. Ariceta: None. Akyoney: None. P20.031.B Hybrid minigene assay: an efficient tool to characterize mRNA splicing profiles of NF1 variants Valeria Morbidoni 1,2, Elisa Baschiera1,2, Monica Forzan2, Valentina Fumini2, Dario Seif Ali2, Gianpietro Giorgi2, Lisa Buson1,2, Maria Andrea Desbats1,2, Matteo Cassina2, Maurizio Clementi2, Leonardo Salviati1,2, Eva Trevisson1,2 1Istituto di Ricerca Pediatrica - Fondazione Città della Speranza, Padova, Italy, 2Clinical Genetics Unit, Department of Women's and Children's Health, University of Padova, Padova, Italy. Consultant/Advisory Board; Modest; LPA, BioMarin Pharmaceutical Inc, MPS. Nosocomial infections can be described as those that occur within 48 hours of entry to hospital, 3 days of discharge or 30 days of surgery. Mattis3, Marisa W. These P/LP variants were found in genes previously associated with the risk of developing sarcomas (CHEK2, EXT1, EXT2, RB1 and TP53), but also in genes where that risk is still unknown (ERCC2/3, TSC2, RAD50, FANCM and others) or is emerging (PALB2, BRCA2). Cardiac features are present in the majority of individuals, with hypertrophic cardiomyopathy (HCM) occurring in approximately 2 in 3. Feedback is currently available for 28/36: Reasonable possible diagnosis (Advanced for investigation) Diagnosis has already been excluded There is a clear alternative aetiology Does not appear to be accurate Patient no longer at the practice # of patients EHR 9 6 10 2 1 Conclusions: This pilot demonstrates that implementation of such a toolis feasible at a population level with promising feedback from service users. van Gassen5 1Centre for Biomedical Ethics and Law, Department of Public Health and Primary Care,KU Leuven, Leuven, Belgium, 2Biomedical Ethics Research Group, Murdoch Children's Research Institute, Parkville, Australia, 3Melbourne Law School, University of Melbourne, Carlton, Australia, 4Leiden University Medical Centre, Leiden, Netherlands, 5University Medical Center Utrecht, Utrecht, Netherlands. Pancaldi: None. These were reviewed and endorsed after confirming no more recent relevant papers had been published. A potentially pathogenic variant in the MFSD8 gene was revealed. C.C. Hung: A. Comparative analysis of target panel and whole-exome sequencing in CBF-AML patients was carried out. We report on a pregnant 42-year-old patient, 23rd gestational week, whose fetus presented with severe microcephaly, IUGR, cleft lip, dilated intestinal loops and mild hydronephrosis. This work is part of the larger GenCOUNSEL study, funded through the LSARP Genome Canada competition with co-funding from: Canadian Institutes for Health Research, Genome BC, Genome Quebec, Provincial Health Services Authority, BC Children's Hospital Foundation and BC Women's Hospital Foundation. Grant references: This work was supported by the Ministry of Education and Science of Russian Federation (Project No. FSRG-2020-0014). All were Caucasians, 11 from Europe, two from North-America. In the experts' statements, professional ethics is a working self-regulatory mechanism. However, little is known about the causal CAD genes and the mechanisms of their action. Results: We collected 334 patients' samples; 99/334 were index cases. Cheshuk: None. It was also revealed that mutations in ARID1A prevail in patients with distant metastases (p = 0.03). Duquette: None. Considering all analyzed 9 genes, OS was significantly longer for patients with detected mutations in cfDNA. Methods: Banding cytogenetic and interphase mFISH with the probe panel for chromosomes 13, 14, 15, 16, 17, 18, 21, 22, X and Y. J.A. Puig-Butillé: None. Conclusion: Genetic analysis changed the diagnosis of an HAE patient provided by biochemical assays. Here, we set out to construct polygenic-risk-scores (PRS) for longevity and to investigate the functions of longevity-associated variants. P24.053.D A Genome-Wide Association Study of Copy Number Variants of sepsis susceptibilityItahisa Marcelino-Rodriguez1,2, Tamara Hernandez-Beeftink1,3, Luis A. Background: Multi-omics analysis can provide novel insights into underlying biological mechanisms of traits and complex diseases. Boute: None. This diagnosis will permit adoption of screening measures in the patient to detect malignant transformation at early stages. Semenova: None. P09.094.C Genetic characterization of 274 patients with neurofibromatosis type 1: rare and diagnostically challenging co-occurrence of two variants in the same patient Rita Bastos Ferreira 1,2, Susana Sousa1,2, Ana Lopes1,2, Ana Filipa Brandão1,2, Sara Morais1,2, Paulo Silva1,2, Fátima Lopes1,2, Alexandra Lopes1,2, Cláudia Patraquim3, Miguel Rocha4, João Parente Freixo1,2, Jorge Sequeiros1,2, Jorge Oliveira1,2 1CGPP-IBMC – Centro de Genética Preditiva e Preventiva, Instituto de Biologia Molecular e Celular, Universidade do Porto, Porto, Portugal, 2i3S – Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal, 3Serviço de Pediatria, Hospital de Braga, Braga, Portugal, 4Serviço de Genética, Hospital de Braga, Braga, Portugal. Conclusion: The results indicate that the Wnt pathway may have a pathogenic function in a group of ALL patients and high LEF1-total expression might be a marker for shorter relapse free survival time in B-cell ALL. Bonneau: None. E.K. Vanhoutte: None. Conclusion: ANK2, AKAP9 and TSC2 reveal the main biological processes suggesting that the cytoskeleton organization in AIS could be involved in severe tinnitus. P.I. Buonfiglio: None. Balthazard: None. Cells were infected with viruses in the presence and absence of TPCK-trypsin, and a significant impact on viral production was not observed. O'Ferrall: None. Aim: To give an overview of our cohort`s clinical phenotype and AXIN2 gene variants. The relative TL values ranged between 0.089-0.607 in TE and between 0.061-0.414 in ICM. For each mutation we investigated osteoblasts in two unrelated patients, one with mild and one with severe phenotype. L.A.J. Kluijtmans: None. Slofstra, Robert Sietsma, Sander Van den Hoek, Martine T. S.M. Hücker: None. Haycock: None. Targeted molecular testing should be offered to the couple in order to reach a diagnosis and assess the recurrence risk for future pregnancies. Conclusions: We established two new cell lines derived from different HNSCC locations that are good models to study this type of cancer. Šarić: None. Ferrero: None. Hojo: None. The predisposition to unhealthy eating habits is described. Morales: A. Egloff: None. Re-analysis of the mother's data showed low-grade mosaicism for this variant, which was below the threshold of the analysis pipeline. Methods: NF1 patients from a large French NF1 cohort were molecularly characterized using next-generation sequencing, microsatellites analysis, and MLPA between 2005 and 2020. Here, we present a family with an affected 1.5-year-old infant, second-born of nonconsanguineous parents, with symptoms of progressive hypokinesia, hypotonia, reduced facial mimicry, diurnal periods of lethargy and irritability, sporadic dystonic movements, developmental delay, and seizures. Annotation and analysis of variants were realized by a homemade interface (PolyWeb). Goals: Improved science literacy and awareness, education, appreciation of science, celebration, inspiration for trainees, students, and the public, international collaboration, and enjoyment. UMAP analyses of the transcriptome were performed and overlapped for each experiment. Some of them have dysmorphia, short stature, epilepsy, microcephaly, deafness, etc.Metabolic screening and karyotype were normal in all patients. Jiao: None. G.A. Rappold: None. Except for one splice site variant, all other were hemizygous missense variants affecting the kinesin motor or PRC1 binding domain of KIF4A. The disease can either occur as part of a syndrome or as non-syndromic, isolated craniosynostosis. Grants: Alex Lemonade Stand Foundation, MiaNeri Foundation, La Caixa Foundation. Alexander disease (AxD) is a leukodystrophy caused by heterozygous mutation in the GFAP gene, presenting at different age of onset: early childhood (type I) and later, up to adult (type II). After haplotype reconstruction, the pathogenetic variant's age estimation was carried out with the DMLE+2.3 software package. Mutations in this gene are causal for various congenital myopathies including malignage hyperthermia and susceptibility RM. Hum Mutat. Evren: None. Our preliminary results suggest that axon guidance pathways, such as the Semaphorin and Netrin signaling pathways, are likely to be involved in the disease pathogenesis, as well as GP6, nNOS and protein kinase A signaling pathways. Hoffmann: None. Gerik-Celebi: None. Truncating variants in the maternally imprinted MAGEL2 gene have been identified in patients with SYS. According to the results of a biochemical blood test, patients were dividedinto two groups: the high-risk group (threshold ≥ 1:100) (n = 338) and the average-risk group (threshold 1:101 - 1:2500) (n = 8567). SEMs can be used as outcome or mediator in association models in order to better understand its contribution to MPM development. L.P. Rweyemamu: None. A.E. Hall: None. Characteristic features of DDX3X-NDD include mild to severe intellectual disability, hypotonia, behavioral problems, movement disorders, dysmorphic features. Introduction: The PI3K pathway is well known for its role in cellular proliferation and survival. Sixty-one percent affected an 'ACMG59'-listed gene. We report a 11-months-old girl with neurodevelopmental delay, hypotonia and minor dysmorphic features (epicanthal folds, left eye ptosis, broad nasal root, rounded forehead, retrognathy and preauricular appendages). miRNAs have been investigated and suggested as important biomarkers for the evaluation of disease, including neurodegenerative diseases. Conclusion. Stefansdottir: None. But less is known about the effect of genetic alterations at XLαs (eXtra Large Gsα), encoded by and alternative exon 1 of the paternally expressed long form of Gsα. LDLR, c.*19G>A, c.*503C>T, c.*517C>A and c.*1227C>T did not show significant differences in luciferase activity with

respect to wild type (WT). Applying battery of molecular genetics tests in routine practice of regional genetics laboratory allowed to perform extensive analysis of CFTR variants in regional CF patients. Materials and Methods: The length measurement of each NDRE gene and its possible repeat expansions was done by PCR, Repeat Primed-PCR (RP-PCR), agarose gel electrophoresis and fragment length capillary electrophoresis. Methods: Northern Europeans from UK Biobank comprising 6,914 cases reporting pain all over the body lasting more than 3 months and 242,929 controls were studied. Castronuovo: None. Guida: None. This gene plays a key role in the phosphorylation of several protein, promoting autophagy. P22.017.D Sudden shift to remote genetic counseling during the COVID-19 pandemic: experiences of genetics professionalsDaniela Turchetti1, Linda Battistuzzi2, Benedetta Bertonazzi3, Lea Godino 1 1Division of Medical Genetics; IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, 2Dipartimento di Informatica, Bioingegneria, Robotica e Ingegneria dei Sistemi, Università degli Studi di Genova, Genova, Italy, 3IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy. Hadj-Rabia: None. Zilovic: None. A recessive disorder was suspected because of previous termination of pregnancy (TOP) for similar abnormalities in a sister fetus. Perea: None. We collected clinical data including phenotype and family history of CHD. The variant (c345G>C) in the ACTA2 gene was found in an index patient with aortic root dilation. A wider (often milder) spectrum of disease severity results from missense mutations, if a partially functional protein is produced. In controls, FKBP6 localized to cytoplasmic granules together with PIWIL1 and TDRKH. Further investigation is needed in order to elucidate all contributing mechanisms that can indicate the severity of the disease. Results: Six patients treated with 5-fluorouracil carrying one level 1A PharmGKB variant in DPYD showed a decrease in drug mean clearance over the follow-up period (p.A (p.Gly537Arg) in the EPAS1 gene, responsible for the development of hereditary erythrocytosis type 4. As PCR removes base modifications, their detection via traditional sequencing technologies requires the use of special library preparation steps to convert nucleotides according to their methylation status. Parents of affected individuals often turn to the internet for information and support. P19.032.D Wright and Malékot assessments of Inbreeding in the populations of North Ossetia with subdivided structure Galina I. Pathogenic compound heterozygous variants were identified in ATP7B gene and NR2E3, responsible for Wilson disease and for Enhanced S-cone syndrome, respectively. One patient has a brother with the same condition. Robles-Bolivar: None. P20.002.A A multi-omics approach to study monozygotic twins discordant for amyotrophic lateral sclerosis Martina Tosi 1, Miriam Zuccalà1, Francesco Favero1, Lucia Corrado1, Roberta Croce1, Chiara Basagni1, Nadia Barizzone1, Laura Follia2, Fabiola De Marchi3, Elena Chinni4, Letizia Mazzini3, Davide Corà1, Maurizio Leone4, Sandra D'Alfonso1 1University of Eastern Piedmont UPO, Novara, Italy, 2University of Torino, Torino, Italy, 3ALS Center AOU Maggiore della Carità, Novara, Italy, 4SC Neurologia, Dipartimento di Scienze Mediche, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Foggia, Italy. Introduction: Syndromic retinal diseases (SRD) are a group of rare and complex inherited systemic disorders, characterized by a challenging molecular study and clinical management. Therefore, this report explores insights on the phenotypic and genotypic spectrum of this rare syndrome. Recently, de novo loss-of-function and missense variants in the gene BICRA were described as causative for a novel autosomal-dominant neurodevelopmental disorder (NDD) in twelve patients. L.A.M. Ferreira: None. G.S. Taylor: None. Møller-Madsen: None. Melli: None. Government's interest in the results of genetic research plays a controversial role. Results: The frequency distribution of alleles and genotypes in all studied groups were corresponded to the theoretically expected according to Hardy-Weinberg equilibrium. X-linked genes belonging to MAGEA family, FLNA and UXT showed a different methylation pattern depending on the gender. Wilson1,3, Nicola Pirastu1 1University of Edinburgh, Usher Institute, Edinburgh, United Kingdom, 2University of Birmingham, Institute of Immunology and Immunotherapy, Birmingham, United Kingdom, 3University of Edinburgh, Institute of Genetics and Cancer, Edinburgh, United Kingdom. Conclusions: p.Arg21Ter associates with lower Lp(a) and is in LD with the more frequent LPA loss-of-function mutation rs41272114 in all investigated populations. Minguez: None. 358_360delGAG and c.35delG. Rapid Diagnostic Tests (RDTs) are equipment-free, can be used by minimally trained healthcare workers generating rapid results. Pijuan: None. Tuncer 1,6 1Istanbul University, Aziz Sancar Institute of Experimental Medicine Department of Genetics, Istanbul, Turkey, 2Istanbul University, Graduate School of Health Sciences, Istanbul, Turkey, 3Istanbul University, Aziz Sancar Institute of Experimental Medicine, Department of Immunology, Istanbul, Turkey, 4Yeni Yuzyil University Gaziosmanpasa Hospital Bone Marrow Transplantation Center, Cell Processing Unit, Istanbul, Turkey, 5Yeni Yuzyil University, Medical Faculty, Department of Medical Microbiology, Istanbul, Turkey, 6Istanbul University, Aziz Sancar Institute of Experimental Medicine, Diabetes Application and Research Center, Istanbul, Turkey, 77Justus-Liebig-University, Clinical Research Unit, Center of Internal Medicine, Giessen, Germany. Frébourg: None. Introduction: Cancer burden is still a globally growing problem. Gestoso-Uzal: None. Methods: mtDNA non-coding region was studied in newly diagnosed sporadic breast cancer patients and healthy controls among Sri Lankan Tamil and Muslim ethnicities (N = 30 pairs each) of the Sri Lankan population. Mironovich: None. Davis: None. Al-Qassabi: None. Finally, mtDNA copy number was not correlated to mutant loads. de Vrieze: None. Calvas: None. Tischkowitz11, S. Odhams: None. Marle: None. B.A.J. Roelen: None. The objective of our study was to investigate the type and frequency of Y-chromosome abnormalities in male infertility. Kuechler2, Christian Bergamini3, Elena Bonora4 1University of Bologna, Department of Medical and Surgical Sciences, DIMEC, Bologna, Italy, 2Institut für Humangenetik, Essen, Germany, 3Department of Pharmacy and Biotechnology (FaBit), Bologna, Italy, 4Department of Medical and Surgical Sciences, DIMEC, Bologna, Italy, 5Institut für Medizinische Genetik und Angewandte Genomik, Tübingen, Germany. Materials and Methods: NGS capture technology allowed us to identify five cases of MFS probands who harbored a mosaic pathogenic variant in the FBN1 gene. We are presenting clinical features in each patient. P17.070.A scMuffin: an R package for resolving solid tumor heterogeneity from single-cell dataNoemi Di Nanni, Cinzia Cocola, Valentina Nale, Eleonora Piscitelli, Alice Chiodi, Ingrid Cifola, Ileana Zucchi, Rolland Reinbold, Luciano Milanesi, Alessandra Mezzelani, Paride Pelucchi, Ettore Mosca Institute of Biomedical Technologies, National Research Council, Segrate (Milan), Italy. P.J. Morrison: None. P09.072.B PRKN exon inversion leads to juvenile generalized levodopa-responsive dystonia Emuna Paz 1, Hagar Mor-Shaked1, Adily Basal1, Simona Ben-Haim2, Hanna Grobe3, Sami Heymann4, Zvi Israel4, Vardiella Meiner1, Montaser Namnah5, Anat Nitzan3, Ann Saada1, Tomer Tzur6, Ronen Zaidel-Bar3, Tamar Harel1, David Arkadir5 1Department of Genetics, Hadassah Medical Center, Jerusalem, Israel, 2Department of Nuclear Medicine, Hadassah Medical Center, Jerusalem, Israel, 3Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv-Yafo, Israel, 4Department of Neurosurgery, Hadassah Medical Center, Jerusalem, Israel, 5Department of Neurology, Hadassah Medical Center, Jerusalem, Israel, 6Department of Plastic Surgery, Hadassah Medical Center, Jerusalem, Israel. Cini Masini: None. Púa Torrejón: None. Patients and Methods: A total of 18 patients with osteosarcoma were enrolled in the study. This investigation showed the origin from chromosome 1. Materials and methods: Monocyte-derived dendritic cells (MDDCs) from PD patients and sex/age matched healthy individuals were generated from PBMCs to characterize their cytokine expression profile after LPS or bacterial stimulation using RT-qPCR and ELISA. W.T.A. van der Graaf: None. M.R. Openshaw: None. Milachich: None. It is an X-linked recessive disorder and occurs predominantly in males. P01.101.A Y-chromosome abnormalities in men with reproductive failure Mariela Hristova-Savova, Kalina Belemezova, Yuri Batchvarov, Petya Andreeva, Daniela Savova, Maria Yunakova, Tanya Timeva, Atanas Shterev, Ivanka Dimova SAGBAL"D-r Shterev", Sofia, Bulgaria. Association between the genotypes in terms of KLK3 gene's SNPs and PSA level were statistically significant among early-stage cancer patients (p = 0.036, p = 0.042). N.R. Singh: None. Our findings are consistent with the literature. A total of 271 patients consulting for evidence-based lifelong premature ejaculatory dysfunction were selected in this study. Clavenna1, Elisabetta Casalone2, Alessandra Allione2, Federica Grosso3, Roberta Libener4, Alberto Muzio5, Ottavio Rena6, Guido Baietto6, Sara Parini6, Renzo Boldorini7, Enrica Migliore8, Dario Mirabelli8,9, Corrado Magnani10, Daniela Ferrante10, Giuseppe Matullo2,9,11, Irma Dianzani1,9 1Department of Health Sciences, Università del Piemonte Orientale, Novara, Italy, 2Department of Medical Sciences, Università di Torino, Torino, Italy, 3Mesothelioma Unit, AO SS. Sagaidak: None. Sonnier: None. Employment (full or part-time); Significant; AstraZeneca. Stefano: None. aureus. Patients with CA genotype and the carriers of A allele had an increased probability of adenocarcinoma histological tumor type, IIIA tumor stage, and pT3 tumors. After variant annotation, we selected genes in which deleterious variants were identified according to their function and the segregation of the variant in affected relatives. Depending on the initial analysis, a new diagnostic variant was identified, or the segregation pattern pointed to a previously identified variant. Conclusion: The case of our patient contributes to the studies of the phenotypes of patients with Keipert syndrome which occur as a result of GPC4mutation. Makukh3, Lilia B. Baietto: None. Pajusalu: None. Genetic analysis revealed three mutations in the GUCY2D gene segregating with the phenotype in the pedigrees. UCAM- Universidad Católica de Murcia, Murcia, Spain, 4Departamento de Pediatría. Routine and modern biochemical diagnostic methods (tandem mass spectrometry (TMS), gas chromatography (GC), high performance liquid chromatography (HPLC)) were used to establish the diagnosis; molecular genetic research. These targets, as well as selected regions based on previous GWAS results, were included in a capture assay, and sequenced in 700 additional ischemic stroke cases from our hospitals. Using Exome sequencing a heterozygous de novo missense variant in HNRNPR, p.Arg588His was identified. Di Maio: None. Cisneros: None. Trujillo-Quintero: None. 358_360delGAG. Reymond: None. CNVs identification aided by the selection of HPO terms, highlights the clinical relevance of those variants in which HPO terms match. Writzl: None. We identified a novel homozygous missense mutation (c.665G>C; p.Gly222Ala) in UQCRC2 coding for structural subunit Core 2 in a patient with severe encephalomyopathy. Cavirani: None. Drouin-Garraud: None. PPI map for genetic modifiers identified in DMD patients was constructed using STRING v11. Stathaki: None. It is considered a principal regulator of the contractile behavior of striated muscle. Brunner4,8 1Shaare Zedek Medical Center, Jerusalem, Israel, 2Braun School of Public Health and Community Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel, 3Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel, 4Department of Human Genetics, and Donders Center for Neuroscience, Radboud University Medical Centre, Nijmegen, Netherlands, 5Estonian Genome Centre, Institute of Genomics, University of Tartu, Tartu, Estonia, 6Institute for Maternal and Child Health IRCCS Burlo Garofolo, Trieste, Italy, 7The Wellcome Sanger Institute, Wellcome Genome Campus, Hinxton, United Kingdom, 8Department of Clinical Genetics and GROW-School for Oncology and Developmental Biology, and MHeNS School for Neuroscience, Maastricht University and Maastricht University Medical Center, Maastricht, Netherlands. Since then, only 9 families were described world-wide, 8 of them consanguineous, harbouring KATNB1 variants in homozygosity. Here, we report three unrelated families clinically diagnosed with STL who present novel biallelic loss of function variants in COL9A3. Anžič: None. While more than 70% of pathogenic variants in TP53 are missense variants, including the most common variant in southern Brazil (TP53:c.1010G>A, p.Arg337His), the vast majority occurs very infrequently, and thus their clinical significance is uncertain or conflicting.Case report: We herein report the cases of two unrelated families with the same genetic variant (TP53:c.718A>G, p.Ser240Gly), which has conflicting interpretations of pathogenicity in ClinVar (variant of uncertain significance vs. Employment (full or part-time); Modest; Sechenov First Moscow State Medical University (Sechenov University). This work is generated within the ERN Euro-NMD F. We aim to continue hearing from participants with final results collated and analysed in May 2021. As far as chromosome 13 is known, it contains about 300 genes that synthesize active proteins. Romero: A. Methods of genetic testing vary and include cerebral MRI, Sanger sequencing or Next Generation Sequencing, Whole Exome Sequencing or Whole Genome Sequencing, SNP array or MLPA. Delanty: None. Ownership Interest (stock, stock options, patent or other intellectual property); Significant; PolyOmica, PolyKnomics BV. Results: The interviews with 13 patients who had (or were carriers of) LQTS and 12 health professionals (clinical geneticists, genetic counsellors, cardiologists, molecular geneticists and patient coordinators) demonstrated that religion was significant in maintaining wellbeing in these patients. Stránská: None. Slep17 1Erasmus MC, Rotterdam, Netherlands, 2Seattle Children's Research Institute, Seattle, WA, USA, 3Greenwood Genetic Center, Greenwood, SC, USA, 4Duke University School of Medicine, Durham, NC, USA, 5Human Genetics and Genome Research Division, Cairo, Egypt, 6Howard Hughes Medical Institute, San Diego, CA, USA, 7Université de Bourgogne, Dijon, France, 8Centre Hospitalier Universitaire de Dijon, Dijon, France, 9Hôpital Robert Debré, Paris, France, 10Université de Paris, Paris, France, 11The Children's Hospital of Philadelphia and the Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA, 12Children's Hospital of Philadelphia, Philadelphia, PA, USA, 13Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom, 14Royal Children's Hospital, Melbourne, Australia, 15University of Washington, Seattle, WA, USA, 16University of Minnesota, Minneapolis, MN, USA, 17University of North Carolina, Chapel Hill, NC, USA. Gega: None. Demurger: None. AZV 17-29622A A. Conclusion: SNPs rs9939609-FTO, VNTR-MAOA, and rs4680-COMT are associated to the risk of obesity only in girls. Yammine: A. Vitobello*: None. Fabbro4, Micaela Galain4, Jorge E. Whether the loss of transcriptional activity is caused by alterations of DNA binding or intracellular localization of SOX4 is currently investigated. P22.036.C Evaluation of nursing and midwifery capacity to deliver genomic healthcare in Wales United Kingdom Joanne Elizabeth Swidenbank 1, Emma Tonkin1, Maggie Kirk1, Siva Ganesh1, Deborah Lancastle1, Mark Davies1, Alexandra Murray2, Michaela John2, Rebecca Hopes2 1University of South Wales, Treforest, United Kingdom, 2Genomics Partnership Wales, Cardiff, United Kingdom. The apoptotic index was calculated, and DNA-methylation was assessed by pyrosequencing. It is important to assess the role of changes and restoration of leukocyte telomere length in CAD patients before and after surgery. S.M. Taji: None. However, no gastro-intestinal defects have been reported. Conclusions: Aβ1-40 excretion level is a promising biomarker for SYS, and could help to better understand its pathophysiology. Seong: None. ARID2 (AT-rich interaction domain 2) is a newly described disease-causing gene encoding a protein belonging to the SWI/SNF complex, an ATP-dependent chromatin remodeling complex which regulates DNA accessibility at the nucleosome and facilitates DNA transcription, replication and repair. Inclusion criteria were diploidy, successful karyotyping, and androgenetic origin of the genome. P12.078.B Variant classification and expert curation: APC as a pilot project and model of the collaborative InSiGHT-ClinGen Hereditary Colon Cancer / Polyposis (ICCP) Variant Curation Expert Panel (VCEP) Stefan Aretz 1,2, Isabel Spier1,2, Xiaoyu Sherry Yin3, John-Paul Plazzer3, Elke Holinski-Feder4,5, Johan T. CNVs detection by read depth-based analysis was performed with VarSeq (Golden Helix). Also, there is a part of variants, which are classified as missense or synonymous variants of uncertain significance, being highly spliceogenic. Next-Generation Sequencing (NGS) using a panel of 17 genes for aortic aneurysms was performed. Funding: 2015/17/D/NZ5/03442, National Science Centre in Poland M. We report here a 16-years old patient, diagnosed with septal hypertrophy (>11 mm thickness) and slight tricuspid valve regurgitation. Following the ACMG criteria and the relation between phenotype and genotype, we concluded that this variant is probably pathogenic and responsible for the neurodevelopmental disorder present in our patient. Pacio-Míguez: None. This analysis will help to further understand the molecular pathways and etiological differences between syndromic and non-syndromic forms. The objective of this study was to identify susceptible HLA alleles and clinical markers for the early identification of severe COVID-19 among hospitalized COVID-19 patients. Results: We found evidence with causal effects of higher vigorous and moderate physical activity, and less sedentary time on reducing BMI (P = 2x10-5, P = 0.002 and P = 0.02, respectively). Results: A total of 328 patients were included with most patients having a left-sided (n = 117; 35.7%) or conotruncal heart defect (n = 94; 28.7%). The importance of metabolic and genetic factors in the development of childhood obesity remains relevant.The aim of this work was to study the association of the polymorphisms LPL Ser447ter (C-G), -250 LIPC G>A and FTO rs9939609 with obesity in children and adolescents from the Rostov region (Russia). Biopsies of native mitral and aortic valve cusps from 12 patients who underwent surgical correction of acquired heart disease of non-infectious etiology were used as control. Hearing loss associated with the deletion in 63 subjects displayed an average age of onset of 30.6 years (SD 14.9 years) and variable audiometric characteristics. Rotter3, Maryam Kavousi2, Jeroen van Rooij1 1Department of Internal medicine, Rotterdam, Netherlands, 2Department of Epidemiology, Erasmus MC, Rotterdam, Netherlands, 3Institute for Translational Genomics and Population Sciences, The Lundquist Institute at Harbor-UCLA Medical Center, Torrance, CA, USA, 4Department of Internal Medicine, Sanford School of Medicine, University of South Dakota, Vermillion, SD, USA. Ursu: None. Mohamed1, Hafsa Al-Emam1, Halla Elshwekh1, Nabil S. Vogel: None. Fst (Fixation index) and iHS (Integrated Haplotype Score) for GWAS SNPs were analyzed with the use of 1000 Genome Selection Browser 1.0 (. Finally, with the effect of grape seed extract, we have seen elevated free radical concentrations improve interleukin (IL10) gene expression levels. Kilpeläinen1 1Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark, 2Molecular Epidemiology, Department of Medical Sciences, Science for Life Laboratory, Uppsala University, Upssala, Sweden, 3Department of Public Health, Section of Epidemiology, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. P17.077.D Exploring the causality of epidemiological relationships between Type 2 Diabetes and cancers using pathway-specific genetic instruments Zhanna Balkhiyarova 1, Anna Ulrich1, Ayse Demirkan1, Liudmila Zudina1, Igor Pupko1, Jared G. Remedios: None. Funding: PIE16/00049,PI19/01835,Roche,CM19/00216,FI20/00031,CB16/12/00234,CB06/02/0073. To compare both approaches, 10 additional patients were studied by whole exome sequencing (WES), using the whole exome family plus test (Blueprint Genetics) or Human Clinical Exome Capture & Mitochondrial DNA (Nimblegen). Results: Female patients developed significantly more sessile-serrated lesions per year than male patients (U = 885.500; p = 0.012). Previously, it has been shown that CRISPs can regulate ion flow via various sperm ion channels, and thus potentially regulate sperm function, including motility. Ramos4, Edward S. Gilly: None. Funding: KESS MAXI 21434 J.E. Swidenbank: None. Nejdl: None. In the mediation analysis, we found evidence for a mediating role of FI (30% mediated, 95% CI = 10-50%, P = 3.11x10-3), bioavailable testosterone (12% mediated, 95% CI = 7-16%, P = 1.92x10-6), and SHBG (7% mediated, 95% CI = 2-12%, P = 2.72x10-3). The aim of this work is to present the diagnostic results of a ADPKD cohort. Smolanka: None. In the case of consanguineous parents, Trio WES should be prioritised with respect to a panel of genes, since parents could be carriers for two or more different autosomal recessive conditions, and in order to fully delineate recurrence risk for prenatal counselling. Pehlivan: None. During inflammation, the rate of telomere shortening is accelerated by increased cell division and increased oxidative stress, leading to cellular senescence. Sawka: None. This test revealed the J2a (J-M410) haplogroup. (2012). Ten actionable PGVs were identified in additional genes (4xATM, 1xCDH1, 1xCHEK2, 2xPALB2 and 2xTP53). The consistent neuropathological diagnosis is FTD-TDP subtype C, with TDP-43 protein aggregates in the temporal cortex and dentate gyrus of the hippocampus. First, we were able to distinguish similar genes, as SMN1 and SMN2 and identify structural variants in genes with similar pseudogenes such as PKD1 or PKD2. Sokolovska: None. Miroshnichenkova: None. Lissencephaly describes a group of clinical conditions characterized by the absence of normal cerebral convolutions and abnormalities of cortical development. Mirabueno: None. E.B. Binder: None. The kinase activity levels were detected by Immunoblot using an anti-phopho-Cdc25C (Ser216). dMMR tumors without a germline variant or MLH1-promoter hypermethylation (Lynch-like) may have two somatic non-epigenetic MMR aberrations (somatic dMMR). Fossoud: None. Poirier: None. Amenta: None. Herrero-Forte: None. By using WGCNA was revealed 15 co-expression modules and identified the driving module for HGSOC associated with the tumour size, the presence of lymph node metastasis and the distant metastasis. Of the initial 97 candidates, 15.5% presented anomalous laboratory results (15/97). P19.031.C Interactions between STAT3 IL10 and IL12B genes polymorphism with viral load among women with human papillomavirus Abbas Hadi Hammadi Albosale southern Federal University, Rostov-on-don, Russian Federation. D.S. Kolobkov: None. Palenzuela3, Georg Auburger2 1Center for the Investigation and Rehabilitation of Hereditary Ataxias, Holguín, Cuba, 2Goethe University Medical Faculty, Frankfurt, Germany, 3Center of Genetic Engineering and Biotechnology, Havana, Cuba. Rial-Sebbag: None. After RNA extraction from all cell-types (fibroblasts, iPSCs, NPCs and neurons), we assessed genome-wide differential expression using expression microarrays. The older patient is under investigation for sleep apnea and has stable T2 hyperintensity in the dentate nuclei on brain MRI. Introduction: Approximately 1 in every 100 couples are at risk of a child with an autosomal recessive condition. Frank: None. Zelinska: None. WebGestalt tool was used for microarray data analysis. Carli: None. Flanagan, Sian Ellard, Andrew T. Mattei: None. Morgan: None. Duchesnay: None. The relationship among these components differentiates informed choice from less informed choice. A.K. Volkov: None. Materials and Methods: In the present case report, it is a female patient, 39 years old, residing in Pouso Alegre, Brazil, in October 2019. Baruffini: None. Conclusion: By using functional genomic annotation data to construct its architecture, we developed an interpretable neural network to analyze multiple omics in a single analysis. Results: The 17p13.1 breakpoint at g.9,819,770 disrupts IVS 1 of GSG1L2, whereas the 19p13.3 breakpoint at 6,573,218, is within a low-complexity region. R.M.H. Wijnen: None. Consultant/Advisory Board; Modest; National MPS Society, Little People of America, BioMarin Pharmaceutical. Hepatomegaly was the most common presentation in type I and VI while "rachitic" like bones was the main presentation in type IV. G.M.H. Abdel-Salam: None. Thirty causal variants, 22 of which novel, were identified in 28 genes. Pro224Leu, p. Conclusion: Pathologic variants and genes for IRDs in Iceland did not resemble those described in ancestral North-Western European nations. Variant confirmation and cosegregation studies were carried out via Sanger sequencing. P13.021.B MicroRNA binding sites and their potential role in human diseaseOlga Plotnikova1, Alexandra Filatova 2, Mikhail Skoblov2 1Moscow Institute of Physics and Technology, Moscow, Russian Federation, 2Research Centre for Medical Genetics, Moscow, Russian Federation. M.S. Aapro: F. Conclusion: This is the first study in literature that succeeded to make an in-frame variation effecting the hot spot arginine residue of TGFBIp in zebrafish. For each pair of genes that shared at least one significant (p T;p.(Arg1225Ter)), and a variant of uncertain significance (c.2794-21C>G) in the KIAA1109 gene predicted to affect splicing. We identified the proportion of pathogenic variant carriers with at least one relevant phenotype, to estimate penetrance among 199,945 exome-sequenced UK Biobank participants. P18.034.D Comprehensive analysis of actionable pharmacogenes based on mining of large-scale data from the Saudi population Dorota Monies 1,2, Ewa Goljan1,2, Mohamed Abouelhoda1,2, Brian Meyer1,2 1KFSHRC, Riyadh, Saudi Arabia, 2Saudi Human Genome Program, King Abdulaziz City for Science and Technology, Riyadh, Saudi Arabia. Materials and Methods: A total of 105 infertile males, with azoospermia, were included in this prospective observational study. Nõukas: None. Employment (full or part-time); Significant; Congenica Limited. However, WES detected the F12 variant affecting function c.983G>T (p.Thr328Lys) in the index and her asymptomatic father. Salmenpera: A. It would be necessary that each country has the same guidelines concerning the HBOC syndrome management. Target panel sequencing of 11 genes encoding cardiac ion channels was performed using PGM IonTorrent. Most of the GTS individuals have comorbid diagnoses, of which obsessive-compulsive disorder (OCD) and attention deficit-hyperactivity disorder (ADHD) are the most common. Pokrovskaya: None. Previous affected sibling was the trigger to seek medical advice in 30% of patients with type II. P18.013.C Phasing of the entire CYP2D6 locus with CRISPR-Cas9 enriched Nanopore sequencing Laurentijn Tilleman, Kaat Rubben, Filip Van Nieuwerburgh Ghent University, Laboratory of Pharmaceutical Biotechnology, Ghent, Belgium. Thus, patients with 10q26 chromosomal deletion need multidisciplinary management strategies from birth. Benefits include delineating novel pathogenic genetic variants and defining genetically homogenous patients as potential investigative molecular therapy candidates. Schon: None. Temtamy: None. Dudakova: None. Sánchez-Soler: None. Oflazer: None. Gentle School of Molecular and Cell Biology, University of the Witwatersrand, Johannesburg, South Africa. Despite thesep findings, the genetics of HGS remains largely elusive and has never been explored in a cohort of young individuals. Altmueller: None. Carmona: None. Conclusion: These preliminary results show that p.(Ser127Arg) gain-of-function variant in PCSK9 could be due to the founder effect in France. The geleophysic/acromicric dysplasia (GD/AD), characterized by short stature, short extremities and joint limitation are described as "the mirror image" of MFS. Mutation G45E in GJB2 gene was detected in 31.25% of reads. Trevisson: None. We sought to identify novel candidate genes associated with the spQRSTa, to improve our understanding of the underlying biology. Emerging evidence suggests that various genetic components can account for these cases according to an oligogenic model. Materials and Methods: Using the MPS method, using the congenital muscular dystrophies target panel, a sample of unrelated patients with a referring SMA diagnosis without deletions in the SMN1 gene (78 patients aged 0 to 2) was studied. Piovesan: None. Whole exome sequencing was performed for variant detection and confirmed by Sanger sequencing. ParcTaulí Hospital Universitari. We present the case of parents carriers with heterozygous deletions in the DFNB1 locus encompassing different parts of the GJB6 and CRYL1 genes and the putative regulatory region of the GJB2 gene, discovered after array-CGH analysis in amniotic fluid (AF) from its fetus. The second patient as well as his brother had bilateral complete cryptophthalmos associated to anophthalmia, microphthalmia and iris coloboma. 64/90 cases included in the further analysis could be classified as solved (original report: 83/90; p T/c.925T>A. Cariati: None. Instituto de Salud Carlos III, Majadahonda, Madrid, Spain. We extracted data about individuals' characteristics, clinical and radiological vascular cerebral phenotypes. Belonogova: None. Stein: None. Introduction: Sexual dimorphism in humans is presented in a variety of forms and affects both physical traits and disease-related phenotypes. Finally, Sanger sequencing was used to confirm familial co-segregation of findings. Moreover, the protein feature and function might be affected via loss of the BTB domain from the start point-173 to end point-297, visualized by 3D constructions of the variants. Hammar: None. Introduction: Breast cancer remains the most common cancer among women accounting for nearly 25% of cancers diagnosed. Leter5, Tom G. Conclusion: The usefulness of liquid biopsy for cancer recurrence and metastasis after surgery shows the clinical need to identify patients at high risk. Results: We found the pathogenic variant c.5218C>T p.(Arg1740Trp) in the SETD2 gene, this variant was determined as de novo with the segregation analysis. S.G. Kaler: B. For a clear understanding of health benefits and costs, data on its outcomes are required: proportions of LS, sporadic MMR-deficient (MMRd) cases, and unexplained MMRd cases. Blood EVs or their miRNA cargo might serve as new minimally invasive biomarkers of treatment response. The interpretation of the effect of structural variants is a challenging problem due to highly variable numbers of gene, regulatory, or other genomic elements affected by the CNV. 2014). Consequently, the proportion of visits made to the site by returning visitors has grown to 28% of the total. Studies suggest that adiposity in childhood may reduce the risk of breast cancer in later life. Guleria, Shalini Nayak, Katta M. The immune interaction between the uterus and the embryo is crucial to achieve a pregnancy. After discharge, she lost follow up. Danila: None. There was no history of hematological abnormalities. In F2, we found an inversion involving the 5' part of MSH6 and the 3' part of the nearby gene ANXA4, explaining the familial history.Inversion detection mandates "augmented" panels or WGS and dedicated tools, but makes a valuable contribution to the diagnostic rate. Astuti: None. Other; Modest; BioMarin Pharmaceutical Inc. Tanteles1,2 1Clinical Genetics Clinic, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus, 2The Cyprus School of Molecular Medicine, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus, 3Department of Cytogenetics and Genomics, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus, 4Department of Clinical Genetics, Archbishop Makarios III Medical Centre, Nicosia, Cyprus. Grants: SAF2016-80888-R; CB16/12/00234; Sara Borrell; PERIS SLT002/16/0037; SLT002/16/00164; Fundación Olga Torres; INVES19022TERR; MSCA. Clause: A. Findings in IC vs. Using a functional genomics approach we provide genetic evidence for the involvement of interferon signalling pathway in complicated appendicitis. Ismail: None. Wright: None. The first laws were adopted in 1994, revised in 2004 and 2011. These studies could, however, be potentially limited by examining the effects of individual genes acting in isolation and not in the context of broader biological networks. Wang: A. Material and Methods: We present a 20-years-old girl who was born after a dichorionic diamniotic twin pregnancy with increased nuchal translucency for this fetus. Atanasoska: None. The liquid biopsy predicts cancer recurrence months earlier than PET imaging. We performed exome sequencing followed by genome sequencing to identify the genetic etiology. The research was supported by the grant of the Russian Scientific Foundation, project № 19-18-00422. Omarov: None. Susam: None. Inbreeding is the most important population-genetic characteristic. Results: The variant rs#1126477 at codon position 29 showed significant association with dental caries (p = 0.04). Qualitative data was gathered from patients' reflective diaries to explore the impact of the deliberation process for a predictive HD test and compared with data from clinical appointments. Phone interviews were conducted with mothers who had undergone PGT during January 2009-March 2020 at King Faisal Specialist Hospital and Research Centre (KFSHRC), Riyadh. T.Y. Pang: A. Ben Signor: None. Introduction: Comprehensive coverage of the proteome remains elusive because of proteoforms arising from alternative splicing, allelic variation, and protein modifications. The implemented bioinformatic pipeline allows a high detection rate of pathogenic variants minimizing the detection of variants of unknown significance. Materials and Methods: The study group included 31 patients (16 men and 15 women) aged 58.90 ± 18.98 years with diagnosis "viral COVID-19 pneumonia" treated at the intensive care unit. Conclusion: A splicing assay for the SCN1A gene was created. The PKD mutation database counts more than 1000 pathogenic variants in PKD1 and about 200 in PKD2 gene. In silico we identified several new pathways, containing genes involved in epigenetic modifications, sumoylation and nuclear-cytoplasmic shuttling, which might influence the mechanisms of disease development. Equally, the importance of haplotype information has become more apparent i.e., to identify compound heterozygous variant combinations as disease-causing candidates.Read lengths and coverage routinely obtained from Nanopore sequencing allow unique mapping across repetitive regions which are enriched in SVs. Furthermore, single reads can span large and complex variation end-to-end and cover multiple single nucleotide variants for phasing.To assess the performance of SV calling and read phasing with Nanopore sequencing, we sequenced the well characterised GM24385 cell line and compared the resulting SV and SNP calls against the Genome-In-A-Bottle truth set. Henshall: None. The screening of the 5'UTR of the gene revealed the presence of a novel heterozygous c.-174C>T variant, segregating with the phenotype. Shadrina: A. Girisha Kasturba Medical College, Manipal Academy of Higher Education, Manipal, India. LINE1-RNAs reappear in T-cells from mTORC1 hyperactivation genetic disease (Lymphangioleiomyomatosis) patients, treated for life with mTORC1 inhibitors,and in dysfunctional T-cells infiltrating colorectal or lung tumors, where LINE1-RNAs depletion rescue T-cell function.Our study uncovers a novel epigenetic mechanism contributing to enforcement of T-cell quiescence and suggests that LINE1 RNAs abundance is critical for T-cell effector function in physiological and pathological contexts. Among the most distinctive features of the patients with Keipert syndrome are: craniofacial and digital abnormalities, learning difficulties and sensorineural deafness. The material of the research: the results of a survey of 800 pregnant women from 16 regions in Russia. The program uses a panel with 109 genes associated with SD. S.J.C.F. Moorlag: None. Friedova: None. Results: Two novel missense mutations p.Leu153Pro, p.Ile151Asn and one new frameshift mutation p.Arg176fs in the VHL gene were identified. Díez García-Prieto: A. Array Comparative Genomic Hybridization (aCGH) technique revealed a duplication of 8p11.23 to 8p11.1. The segment duplicated had 6.4 Mbp and involved 62 genes. P08.055.A NFIB - associated intellectual disability and/or speech delay: first report of two novel structural variant disruptionsConstantia Aristidou1,2, Marselia Pantelidou1,2, LUDMILA KOUSOULIDOU 1,2, Athina Theodosiou1,2, Ioannis Papaevripidou1, Sofia Kitsiou - Tzeli3, Niels Tommerup4, Carolina Sismani1 1Department of Cytogenetics and Genomics, The Cyprus Institute of Neurology and Genetics, NICOSIA, Cyprus, 2The Cyprus School of Molecular Medicine, Nicosia, Cyprus, 3Department of Medical Genetics, Medical School, University of Athens, Athens, Greece, 4Wilhelm Johannsen Centre for Functional Genome Research, Department of Cellular and Molecular Medicine, University of Copenhagen, Copenhagen, Denmark. Y.L. Lin: None. Schiller: None. Markowetz: E. Somatic activating mutations of the HRAS gene are associated with various neoplasms. In addition, we compare the clinical phenotype between all currently known YIF1B cases to further delineate the mutational landscape and the clinical phenotype associated with this new disease entity. CRP-levels are significantly affected by genetic variation. Harkness3,5, Helen J. Comparison of array vs. Fazaal: None. Gautier: None. M.P. van den Berg: None. van Asperen1, Peter Devilee1, on behalf of the HEBON study 1Leiden University Medical Centre, Leiden, Netherlands, 2University of Cambridge, Cambridge, United Kingdom, 3Erasmus MC Cancer Institute, Rotterdam, Netherlands, 4Netherlands Cancer Institute, Amsterdam, Netherlands. Isoform specific analysis are being performed using targeted long-read sequencing. Ornelas-Loredo: None. Krauss1, Aras N. Introduction: Hirschsprung disease (HSCR) is a neurocristopathy, characterized by an absence of enteric neurons in the distal part of the bowel. Udaondo", Buenos Aires, Argentina, 5Bioinformatics Platform, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas yDigestivas (CIBEREHD), University of Barcelona, Barcelona, Spain, 6Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Gastroenterology Department, Biodonostia Health Research Institute, Basque Country University (UPV/EHU), San Sebastián, Spain. The variant c.8710G>C was predicted to be deleterious by in silico analysis. No amplification of exons 1 and 9 of the CRPPA gene was observed, confirming the findings of aCGH. Material and Method: 29 patients from 28 different families with a pre-diagnosis of VWD were included in the study. Materials and Methods: The 17 KTCN patients undergoing cross-linking procedure and 5 mild myopia patients undergoing refractive error correction (non-KTCN controls) were ascertained. Quibel: A. Maher: None. The fetuses died and the placentas had hydatidiform moles criteria. Results: Table 1 shows the different subgroups and their acceptance of different applications. A.N. Mattis: None. Tinsley: None. To assess the role of rare variants, we studied one of the largest MS multiplex families with 5 affected members. Introduction: Knee osteoarthritis (OA) is the second most common structural OA disorder affecting approximately 22.9% of individuals 40 years and over globally. Using this data, we can determine the type and frequency of pharmacogenetic defects in Bulgarian population with high impact on prediction of adverse drug reactions and health care consequences. Next, we edited the c.337delG mutation at the exogenous EGFP gene in the HEK293T. A correct MODY diagnosis might change the treatment and reduce the risk of diabetic complications. SNPs were genotyped by PCR-RFLP. Introduction: Characterization of naturally occurring, cytogenomically visible or cryptic structural variants associated with human disorders is important for identifying pathogenic alterations that otherwise could be difficult or impossible to identify. Brahem: None. Levi: None. Ferrero1 1University of Torino, Torino, Italy, 2Istituto Auxologico Italiano, Milano, Italy, 3University of Bologna, Bologna, Italy, 4Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy, 5Federico II University, Napoli, Italy, 6"Sapienza" University of Rome, Roma, Italy, 7Bambino Gesù Children's Hospital, Roma, Italy, 8Università degli Studi della Campania "Luigi Vanvitelli", Caserta, Italy. Transcriptomic signatures of TSs and oncogenes were compared between the tissues and correlated with their respective cancer mutational burden. Manninen: None. Zacher: None. J.C. Wester: None. Conclusions: We clustered all HINT1 mutations in three different structural groups allowing for a potential patient stratification strategy for future treatments. A phenotypic score of extracutaneous manifestations was calculated to assess the disease severity. Conclusion: Providing patients with clear medical information could alter their perceptions of the cause of diagnosis, which could contribute to better outcomes. Results: The investigation of 25 genes of epigenetic regulation using the custom targeted NGS-panel and genomic databases revealed functional transcripts in their introns, including both known (linc00847 (EZH2), SIRLNT (SIRT1), TERT (SMARCA4), PROX1-AS1 (PROX1)) and previously undescribed lncRNAs (HDAC2-AS2 and LOC101929089). Ruiz, Roser Martínez-Rubio, Amparo Girós-Pérez, María Sánchez-Ibáñez, Sergio Lois, Oscar Rodríguez, Ángela Arilla-Codoñer, Cristina Torres-Vidal, Norma Aliaga, Laura Cano, Ángela Gaspar, Ana Perpiñán-López, Nuria Serrano, Clara Casañ, Celia Buades-Gomis, Alejandro Romera-López, Cristian M. Introduction: Triple-negative breast cancer(TNBC) is the most aggressive and carries the poorest prognosis, largest recurrence and lowest survival rate. In 2 cases with genotype [p.L541P, p.A1038V] and mutation p.G1961E was found «mild» phenotype. Tournier: None. P12.152.D Analysis of BARD1, PRDM9, RCC1, and RECQL in patients with ovarian cancer by targeted next-generation sequencing of DNA pools Malwina Suszynska 1, Magdalena Ratajska2,3, Aleksandra Ryszkowska1, Jaroslaw Debniak4, Dariusz Wydra4, Cezary Cybulski5, Bartosz Wasag2,6, Piotr Kozlowski1 1Department of Molecular Genetics, Institute of Bioorganic Chemistry, Polish Academy of Sciences, Poznan, Poland, 2Department of Biology and Medical Genetics, Medical University of Gdansk, Gdansk, Poland, 3Department of Pathology, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand, 4Department of Gynaecology, Oncologic Gynaecology and Gynaecological Endocrinology, Medical University of Gdansk, Gdansk, Poland, 5Department of Genetics and Pathology, International Hereditary Cancer Center, Pomeranian Medical University, Szczecin, Poland, 6Laboratory of Clinical Genetics, University Clinical Centre, Gdansk, Poland. Prontera: None. Souche: None. Au: None. Lejeune: None. Martynov1, Roman V. Musa1, Mahmoud E. Materials & Methods: In fibroblasts from SYS and PWS patients and healthy controls, we analysed the excretion levels of amyloid-β 1-40 peptide (Aβ1-40). The novel pathogenic variant identified in the patient was associated with a particular phenotype specifically in regards to retinal pigment deposits, yet with normal male genitalia. The XIST locus (in cis) on each additional X chromosome initiates its silence, making it an inactive X. Bourbon: None. Other demographic and clinical variables (including multiply affected family, coexistence of epilepsy, autism spectrum disorder, abnormal brain imaging or microcephaly) were not significantly associated with WES yield. The study included 20 MF patients diagnosed using clinical examination and histopathological and immunohistochemical skin biopsies tests. Terradas: None. Despite a partial phenotypic overlap, 8q21.11 microdeletion syndrome should be considered as a distinct entity. Macville: None. The accurate genetic diagnosis has a great impact on decision making for clinical management of these patients, offering in the affected patients PGT-A or sperm donor. Frias: None. Chaumette3, J. Genome-wide association studies (GWAS) have identified thousands of genetic variants that are associated with complex traits. Acknowledgement: The study is a part of a project KP-06-N33/5 from 13.12.2019 - NSF of Bulgaria. Results: We identified 21 studies, including data from 336 genotyped patients with NS. A.K. Büscher: None. of Pediatric Endocrinology, Hospital Universitario La Paz, Madrid, Spain, 4Dept. Q. Trump: A. A major tendency to autoimmune phenomena than to immunodeficiency was recorded in patients as demonstrated by the finding of circulating autoantibodies, low levels of CD8 T cells and high levels of inflammatory cytokines. P22.022.A Psychological burden of preimplantation genetic testing (PGT) on mothers with multiple monogenic disorders and the role of genetic counselling in Saudi Arabia Monira AlShehri 1, Alya Qari1,2, Moeenaldeen AlSayed1,2, Ameera Balobaid1,2, Wafa AlQubbaj1,3 1Alfaisal University, College of Medicine, Riyadh, Saudi Arabia, 2Department of Medical Genetics, King Faisal Specialist Hospital and Research Centre (KFSH&RC), Riyadh, Saudi Arabia, 3Department of Pathology and Laboratory Medicine, King Faisal Specialist Hospital and Research Centre (KFSH&RC), Riyadh, Saudi Arabia. Pollard: None. Materials and Methods: We investigated all the members of 3 families in which 9 patients showed both sensorineural hearing loss and RP. We performed whole-exome sequencing of constitutive material from 38 cancer-affected patients from 33 families at risk for FCCTX (following Amsterdam I clinical criteria). Rega: None. Funding: CIBERER (06/07/0036), IIS-FJD BioBank (PT17/0015/0006), RAREGenomics-CM (CAM, B2017/BMD-3721), CAM (PEJD-2018/BMD-9544), ONCE, Ramon Areces Foundation, Conchita Rabago Foundation, the University Chair UAM-IIS-FJD of Genomic Medicine, ISCIII (PI16/00425, PI19/0321, FI17/00192 and CPII17/00006) and FEDER. Lebeurrier: None. Moreover we identified two affected siblings raising the total number of genetically confirmed CANVAS cases to 7. Despite being considered a benign condition, epidemiological evidence shows that women with endometriosis develop more frequently certain types of gynecological cancers, including endometrial, breast and ovarian carcinomas. Results: Both patients underwent Whole Exome Sequencing. To our knowledge, this variant is not reported before, and it is absent in the general population in the control databases. N.M. Debes: None. Interestingly, the 18 cases carrying CNTN5 missense variants are highly enriched for mRS = 6 (p-val A P DNAI1 c.48+2dupT P Right atrial isomerism, right-sided aortic arch, AVSD, (sub)valvular PS Y Y GDF1 c.681C>A, p.(Cys227*) P GDF1 c.681C>A, p.(Cys227*) P Dextrocardia, right isomerism, univentricular heart, AVSD, TAPVR N Y PKD1L1 c.2027C>T, p.(Pro676Leu) LP PKD1L1 c.5728C>T, p.(Arg1910Trp) LP TGA, VSD N N GDF1 c.681C>A, p.(Cys227*) P Truncus arteriosus, VSD N N NKX2-6 c.455dupA, p.(Gln153Alafs*?) P NKX2-6 c.455dupA, p.(Gln153Alafs*?) P PLD1 c.2191A>T, p.(Arg731*) P CEP290 c.133_136delCAAG, p.(Gln45Lysfs*3) P Truncus arteriosus, interruption of the aortic arch N ? The LPA gene (encoding apolipoprotein(a)) explains >90% of Lp(a) variance. P11.018.D Clinical and molecular characterization of Beckwith-Wiedemann spectrum patients conceived through assisted reproductive technology Diana Carli 1, Jennifer Spina1, Silvia Russo2, Guido Cocchi3, Donatella Milani4, Elisabetta Prada4, Daniela Melis5, Luigi Tarani6, Marina Macchiaiolo7, Angela Sparago8, Laura Pignata8, Pierpaola Tannorella2, Simona Cardaropoli1, Andrea Bartuli7, Andrea Riccio8, Alessandro Mussa1, Giovanni B. Results: Higher cfDNA concentration was associated with poorer overall survival (OS). K: None. Results: According to clinical signs, patients with congenital aniridia were distributed: the presence of complete or partial aniridia, nystagmus, keratopathy, cataracts and glaucoma. Case report: We report on a 6-year-old boy who was referred for genetic evaluation because of global developmental delay and a severe autism spectrum disorder. Materials and Methods: Next-generation sequencing analysis of glomerulopathy and chronic kidney disease related genes panel was performed in Polish patients with suspected AS. Joly-Beauparlant: None. Introduction: Orofacial clefts is the most common craniofacial anomalies. The list was subjected to functional enrichment analysis yielding 313 genes from the Gene Ontology "lipid binding" molecular function group. Crosby1 1Institute of Biomedical and Clinical Science, RILD Wellcome Wolfson Centre, University of Exeter Medical School, Exeter, United Kingdom, 2Peninsula Clinical Genetics Service, Royal Devon & Exeter Hospital, Exeter, United Kingdom, 3Department of Ophthalmology, University of Arizona College of Medicine, Tucson, AZ, USA, 4Department of Cardiology, Royal Devon and Exeter NHS Foundation Trust, Exeter, United Kingdom. Conclusion: This study broadens the clinical and molecular spectrum of FKBP14-related kEDS with three non-related individuals and two new pathogenic variants. Results: Analysis of CNVs in CAKUT included four studies counting more than 2500 patients. The other rare variant [(NM_005211.3):c.1771G>A (p.Gly591Arg)] was detected in a female patient. De Paolis: None. M.D. García-Malo: None. A neuromuscular gene panel analysis was requested on a two week old male infant, requiring respiratory support, with hypotonia, bilateral talipes and central apnoeas. The aim of this study is to demonstrate the personalized, genetic-based approach to normalize patients' weight and eating habits. These data suggest that a shared genetic basis for Covid-19 and AGA exists in specific pathways, posing interesting links between the pathophysiologies of both traits. These individuals displayed congruent clinical features of motor developmental delay (12/13), speech delay (12/13), behavioral disorders (12/13), intellectual disability (10/13), brain neuroanatomical findings (7/13), and epileptic disorders (6/13), although phenotypes were variable, even within families. Potocki-Lupski syndrome (PTLS) (MIM: 610883) is a microduplication disorder caused by copy-number gains spanning the dosage-sensitive gene RAI1. Broyde: None. Aghayev: None. We investigated this in a large population-based study. Confirmatory chromosome analysis showed a 46,XX,del(13)(q12.3) karyotype. These regions contain highly similar paralogous alleles (>99% identity) that span kilobases within the human genome. Barbosa: None. Heterozygous HNF4A variant c.704G>T was found in two unrelated patients with previously diagnosed diabetes and family history. Introduction: This study reports on the acceptance of human germline gene editing (HGGE) among visitors and non-visitors of 25 public dialogues in The Netherlands. Beyond the link between pathogenic mutations and diseases development, our findings point towards an expanded role of the mitochondrial genome in human phenotypic variation. Introduction: In the past years, we have witnessed a remarkable technological evolution in genetic testing. Turkina3, Sergey I. 45 respondents declared that there are guidelines in their own country concerning the management of BRCA carriers. Westra: None. No significant association between XFS and LOXL1 rs16958477 and rs7173049 SNPs and CACNA1A rs4926244 was observed. Soejima: None. Our patients will contribute the phenotype-genotype correlations in this syndrome. Schaaf-Yang Syndrome is characterised by neonatal hypotonia, developmental delay, intellectual disability, feeding problems in infancy, joint contractures and autism spectrum disorder, sharing clinical overlap with Prader-Willi Syndrome and Chitayat-Hall syndrome. Introduction: Multiple Sclerosis (MS) is a complex disease with high heterogeneity in terms of clinical presentation and treatment response. The mutated residue is highly conserved, and its substitution is predicted to be pathogenic by in silico prediction methods. Satkın: None. Bjerrelund: None. Speakers Bureau/Honoraria (speakers bureau, symposia, and expert witness); Modest; Italfarmaco, Uriach. Antolín: None. Moreover, we suggest some new directions for improving recruitment, retention and safeguarding strategies in biobanking. Background: Copy Number Alterations (CNA) play an important role in cancer and mendelian diseases. Kaminskyi2, Tetjana V. The Leucine in codon 1130 was highly conserved between species and between tyrosine kinases. The stopgain variant is previously unreported, has very low frequency in population and creates a premature stop codon NP_001155252.1:p.(Arg430Ter), thus has been classified as pathogenic. We performed exome-sequencing with subsequent karyotyping and FISH-analysis. Experiments in chick embryos showed that the mutant protein (CDC25B with Pro350) affects the cell cycle and neurogenesis. Incorporating multiple genes, grouped by pathways, has the potential to increase power of discovery while improving our understanding of the underlying biology. Pure trisomies and tetrasomies are the hallmark of hyperdiploid (>47 chromosomes) ALL in children. Vorontsova, Arfenya E. Linn: None. Watson: None. Conclusions: It was found that BGLAP HindIII polymorphism is associated with decreased risk of insulin treatment in Ukrainians with T2DM. Piñero Fernández: None. Ownership Interest (stock, stock options, patent or other intellectual property); Significant; Invitae. Catapano: None. Then the patients were evaluated with the PANSS in terms of symptom severity. abnormal genetic tests results. Telemedicine has proven useful and opens up new strategies to multidisciplinary follow-up in RD. A significative proportion of TUDP patients have putative pathogenic mutations in genes not fully characterized /not associated with Mendelian diseases. Patients with CD38(rs3796863) CC genotype who have reported father's alcoholism were less likely to be in moderate and good social performance group (OR = 0,26, 95%CI 0,20-0,34). To assess the involvement of SEMA6B in this phenotype, we initiated in vitro functional studies in HEK cells and in mouse primary hippocampal neurons. Results: A user can submit one or more lists of variants which are daily re-annotated using external resources accessed through API, such as MyVariant.info annotation API providing links to variant annotations from gnomAD, COSMIC, ClinVar, CIViC, and many others. In addition, one patient had premature termination variant in the PKP2, and the patient with the TNNT2 mutation had additional frameshift variant in the DSC2. For ITFG2, preliminary data are promising since the TR was observed only in patients and in none controls. Mean scale of impulsiveness was also higher for boys (p = 0.010) carrying 3R allele of low transcriptional MAO-A activity. (NM_001098623 GRCh37:hg19: Chr1:228560464 exon 94 c.21989_22002del p. Results: Preliminary results suggest that >90% of clinical genetic variants can be determined by arrays. All analyses were adjusted by age, sex and years of education. Patient1(P1) was clinically diagnosed with NHS at 15 years, due to bilateral cataracts and microcornea, Hutchinson incisors, mild intellectual defect. Carvalho: None. More than 33 genes are related to albinism and these can explain the genetic background of 70-75% of all albinism cases. Fizazi: F. Orlova: None. Steyaert: None. Conclusions: We provide evidence for pathogenicity of 14 mtDNA variants and describe six novel variants with potential causal association. Results: Total of 117 CFTR alleles were revealed (see Table), among them 6 major regional mutations covering 69.2% of all alleles, with most frequent [delta]F508 variant. M.E. van Gijn: None. In the remaining five patients even though their breakpoints were successfully mapped, no molecular explanation was found to explain their respective phenotypes. Karnstedt: None. Elshwekh: None. To avoid possible bias caused by different chromatin condensation, TLs were assessed as relative values by dividing the telomeric fluorescence by the fluorescence of reference region (21q22.13-q22.2) measured in ImageJ 1.51i. Parenti: None. P15.020.D Extracellular vesicles with specific surface proteins are associated with decreased body fat and obesity Ranran Zhai 1, Xia Shen1,2, Lu Pan3, Zhijian Yang1, Ting Li1, Zheng Ning1,3, Yudi Pawitan3, James F. Conclusions: Our study shows that frameshift mutation in KCNB1 gene can cause intrafamilial phenotypic variability and relatively milder clinical findings in these patients. Y.S. Aulchenko: A. Autopsy confirmed ecographic findings and additionally revealed microstomia, tongue agenesis and fusion of five thoracic vertebras, corpus callosum agenesis, esophageal atresia type III. Individual labs in isolation typically lack sufficient data to undertake informative case-control analyses. Results: Karyotyping of the cells lines by G banding revealed a moderate hyperploidy for both cell lines. Other frequent clinical signs were hypospadia (~85 %), brain anomalies (100% of 11 images evaluated) and learning difficulties (42%). Piceci-sparascio: None. Functional profiling showed deregulated GO annotations in C9ALS/FTD patients including 11 genes involved in Generation of neurons and Neurogenesis biological processes and 5 genes involved in Postsynapse cellular component GO annotations. Lou: None. Hermosa-García: None. Conclusion: This genetic testing service was implemented as a routine practice with a simple development and interpretation process that could be offered for any paternally-inherited or de novo SGD. Al-Hassnan: None. Ben Ayed: None. Funding: Aarhus University; Health Research Foundation of Central Denmark Region (A2602); Helsefonden (20-B-0065). Employing a dialogue model, as opposed to debate, the moderator invited participants to exchange perspectives and assemble thoughts, feelings, doubts and questions. The study of the microRNA expression profile in healthy women at different stages of gestation and different types of biomaterial was carried out. Galehdari: None. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Modest; Soleno Therapeutics, Inc, OPKO Health. Inyushkin 1, Valentina D. Hitzert1, Rosalie L. Bioinformatic analysis was performed using BWA and GATK algorithms, the VarAFT annotation and filter tool and ExomeDepth for CNV detection. The two mothers were investigated by WES disclosing novel pathogenic variants, respectively in PADI6 and NLRP2. Biochemical analysis usually shows low serum testosterone, high serum follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels with impaired spermatogenesis. Parallel processing of samples through automation can help to rapidly create NGS libraries with minimal hands-on time. Results: At this moment, genomic analysis through WES was performed in 140 patients. Results: In postnatal life, expression of LMX1B is restricted to poor accessible tissues. 21-75-20120). Identifying sample mix-ups in biobanks is essential to allow the repurposing of genetic data for clinical pharmacogenetics. P11.061.C Variant in HNRNPR leading to developmental delay with facial dysmorphism and bone abnormalities: a case report Marie Massier 1, Marta Spodenkiewicz1, Nathalie Bednarek2, Boris Keren3, Emilie Landais1, Lucas Hérissant1, Céline Poirsier-Violle1, Martine Doco-Fenzy1 1Department of Genetics, Reims University Hospital, Reims, France, 2Department of Pediatrics, Reims University Hospital, Reims, France, 3Department of Genetics, La Pitié-Salpêtrière Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France. Antonucci: None. Brugrada: None. Angelova: None. P17.072.C SVInterpreter: a web-based tool for structural variants inspection and identification of possible disease-causing candidate genes Joana Fino 1, Bárbara Marques1, Zirui Dong2, Dezsö David1 1National Health Institute Doutor Ricardo Jorge, Lisbon, Portugal, 2Chinese University of Hong Kong, Hong Kong, Hong Kong. Carrilho: None. Oocyte aneuploidy incidence was correlated with the reproductive histories of female partners. The research was partially supported by RSF grant №17-15-01051 and within the state task of the Ministry of education and science of Russia. P03.039.C Next generation sequencing in the diagnostic approach to autosomal dominant polycystic kidney disease Deimante Brazdziunaite 1, Marius Miglinas2, Algirdas Utkus1 1Department of Human and Medical Genetics, Institute of Biomedical Sciences, Faculty of Medicine, Vilnius University, Vilnius, Lithuania, 2Center of Nephrology, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania. Gazic: None. Pisciotta: None. Sinnot-Armstrong et al. Males who were found having Normal 46,XY Karyotype were further tested for Y chromosome micro-deletion by PCR. These data support a Clan Genomics model for disease in a population. Raas-Rothschild: None. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Significant; Lundbeck Foundation. Klaassen: None. P09.123.D Clinical and genetic characteristics of two patients from Russia with SESAME syndrome due to mutations of the KCNJ10 gene Natalia Semenova, Olga Schagina, Andrey Marakhonov Reseach Center for Medical Genetics, Moscow, Russian Federation. While NOTCH3 is the best-known gene, several others have been reported, with less data about their associated phenotypes. Analyzing how these professionals integrate genetic testing into the patient-provider relationship is essential to paving the way for a better use of genomics by all. McEntagart: None. All investigated samples were ALK negative. However, the involvement of other cellular mechanisms is unknown. The odds ratio (OR) of case athletes harboring rs1107946 TT genotype compared to CON was 5.09 (95%CI:1.27-20.43, p = 0.022). Variable degrees of peripheral retinal spots (that were easily detected on widefield retinal imaging) were observed in all study subjects. Periodically searching the medical literature for new gene-disease associations; 2. Wenger: A. M.M. Van den Heuvel-Eibrink: None. J.C. Kalanithy: None. Guseva1, Natalya A. Schmidts: None. P08.071.A STAG1 gene heterozygous de novo variant in a patient with Angelman syndrome like phenotype Kristi Rähn 1, Kai Muru1,2, Sander Pajusalu1,2, Eve Õiglane-Šlik3, Katrin Õunap1,2 1Department of Clinical Genetics, United Laboratories, Tartu University Hospital, Tartu, Estonia, 2Department of Clinical Genetics, Institute of Clinical Medicine, University of Tartu, Tartu, Estonia, 3Children's Clinic, Tartu University Hospital, Tartu, Estonia. Manuela Costa: None. Thomas: None. Chumachenko: None. We report the results of a GWAS on fingolimod-treated relapsing-remitting MS patients. The study was supported by the Ministry of Science and Higher Education of the Russian Federation. Results: Credit and recognition, the potential misuse of data, loss of control, lack of resources, socio-cultural factors and ethical and legal barriers were identified as elements that influence decisions on data sharing. Conclusions: CNV analysis from WES data has potential to increase the diagnostic yield in the PAD cohort substantially. Precipitated in 2016 by the BRCA Challenge, all 19 English NHS molecular genetics laboratories now regularly submit pseudonymised individual-level variant data to the National Cancer Registration and Analysis Service of Public Health England (PHE). Materials and Methods: We performed expression profiles of DCM (n = 15) and control (n = 12) samples from left ventricle (LV) using array-based techniques and integrated the differentially expressed miRNAs with the global mRNA expression profiling. Noval: None. Fussey: None. Affected patients present a broad clinical phenotype with dysmorphism, short stature, skeletal and urogenital anomalies. Current scientific evidence was reviewed. However, only few were confirmed to disrupt splicing by a valid splicing assay. Miozzo: None. Mutations of TGFBI affecting arginine residue on the 124th position were reported as one of the hot spots for this group of corneal dystrophies. Pilarova, R. However, a complete and long-lasting response to the ALK inhibitor is rare and patients become resistant to the therapy following an initial response. It is a syndrome of cellular proliferation and apoptosis, and it's manifested by a hypercellular bone marrow with cytopenias and affects multiple lineages. With minimal upfront cost of implementation, PIPseq is easily implemented in any molecular research lab, and democratizes the accessibility of scRNA-Seq across many applications. Rodriguez-Gil: None. Maternal grandmother died due to a brain tumor at the age of 47. Fortunately, the delivery efficiency could be increased using sgRNA and Cas9 protein in form of the ribonucleoprotein (RNP) complex. Our analysis strategy is based on 4 key principles: 1) it is only offered as follow-up NGS testing after WES-based gene panel diagnostics is negative, 2) it is offered as a trio-analysis with healthy parents, 3) a specific variant/gene filter strategy based on inheritance is used and 4) a consequent analysis strategy with stepwise decision points and scheduled consultation moments is also used. To analyze the effects of SOX3 overexpression on the proliferation, viability, migration and invasion of GBM cells, immunocytochemistry, MTT and Transwell assays were employed, respectively. Here we assessed the potential of nanopore sequencing (NS) to characterize whole genome 5'-mC using native DNA. Manor: None. Darmency: None. Bernardini: None. Hearing loss was progressive in 30%, fluctuating in 30% and temperature-sensitive in 22%. Elseed1, Arwa M. S.B. Santos: None. Dr. Paraskev Stoyanov", Varna, Bulgaria. Cultural differences could have an impact of which symptom trigger the patient to seek medical advice. For each genus, cohort-specific results from linear regression models corrected for age, sex, genetic ancestry and asthma were meta-analysed. These findings support the need of increasing the number of families tested and/or the analysis of affected tissues. Brüggenwirth1, Stina Lou3, Ida Vogel3,4,5, Vyne van der Schoot1, Iris M. We aimed at exploring the association of genetic/genomic knowledge, self-epistemic authority (SEA) and perceived importance of genetic/genomic in nursing, and the integration of genetic/genomic skills into nursing practice. Ranza: None. We hypothesize, that performing multi-omic analyses during CPT gives the opportunity to home in on molecular mechanisms involved. Results: IFs were identified in 0.58% (95/16,482) of index patients. Introduction: DNA methylation markers have been proposed as a predictor of biological age. Castellví-Bel: None. Adding the two GRSs that remained independently associated with CAD, GRSs for low-density lipoprotein and for triglycerides, did not significantly improve risk stratification (AUC of 0.759, P = 7.0 x 10-2, HR [CI] of 16.6 [10.4 - 26.4]). Amitrano: None. Conclusions: Preliminary results indicate that in many AEFI patients the vaccine can only trigger neurological symptoms that would have manifested anyway as a result of a pathogenic mutation in a gene engaged in neurodevelopment. Cabrejas: None. Anderson: None. Our findings demonstrate that RNA-seq has a strong potential to improve the systematic detection of fusion genes in clinical applications and provides a valuable tool for fusion gene discovery. P17.087.B High-definition likelihood inference of heritability and genetic correlation on the X chromosome Jiantao Chen 1, Zheng Ning2, Xia Shen1 1Sun Yat-sen University, Guangzhou, China, 2Karolinska Institutet, Stockholm, Sweden. Materials and Methods: Preimplantation genetic testing was performed for 55 couples. P03.008.D Novel CTLA4 heterozygous mutation in a family with type 2 autoimmune polyendocrine syndrome Federico Romani 1, Emanuele Micaglio1, Filippo Martinelli Boneschi2, Giorgio Nevio Casari3, Sara Benedetti3, Paola Carrera3, Carlo Pappone1 1IRCCS Policlinico San Donato, San Donato Milanese, Italy, 2IRCCS Ospedale Maggiore Policlinico, Milan, Italy, 3IRCCS San Raffaele Hospital, Milan, Italy. Methods: This is a descriptive cohort study of Malaysians diagnosed with Kabuki syndrome in Hospital Kuala Lumpur. Murch: None. Early onset myopathy, areflexia, respiratory distress, and dysphagia (EMARDD, OMIM: 614399, MIM: 612453) is a rare autosomal recessive disorder caused by biallelic mutations (at homozygous or compound heterozygous status) in MEGF10 (multiple epidermal growth factor-like domains protein family). Results: We identified 384 rare (MAF C, p.(Leu6267Pro), rs184723737 in NEB in both patients. Conclusions: Cascade testing is a prolonged process as evidenced by the fact that one of the cases tested was a 5th degree relative of the proband. Results: No causative single nucleotide variants were detected in SLC4A11, OVOL2 or any other gene. Both HCM and HeFH can lead to severe heart failure and sudden cardiac death. Materials and Methods: A multiplex sequencing panel targeting 100% of coding bases plus flanking regions for 420 genes was created with Ion AmpliSeq™ Designer and data analysis was perfomed using Carrier Reporter Software. Sriha: None. Materials and methods: over the past 10 years, 1754 patients with mitochondrial dysfunction. The experts ranged from charities, public engagement professionals and medical professionals from the UK and internationally. We find that due to the high lifetime risk of ALS and low frequency of pathogenic alleles, even the current largest genomics projects will struggle to confidently identify intermediate penetrance rare variants in ALS. Conclusions: In general, providers found the patients' viewpoint the most important in assessing appropriateness of PGT. FTT found increased risk scores of 1:102 and 1:2 for trisomy 21 and 13/18 respectively. CRISPR-Cas9 plasmid with spCas9(1.1) gene and sgRNA cassette targeted to the mutated GFP sequence was co-transfected with peGFPmut plasmid with eGFPmut gene under CMV-promoter. ARCI hiPSC-bKs showed more severe defects, with downregulation of several genes involved in epidermal ceramide metabolism. CRTAP gene is associated with osteogenesis imperfecta type VII, while GNS – with mucopolysaccharidosis type III D. Here we refer to two patients with MLID and Beckwith-Wiedemann syndrome (BWS, OMIM # 130650), an overgrowth ID. In 15 cases the identified pathogenic variant occurred "de novo", two times an autosomal variant was found to be of maternal origin with probably incomplete penetrance. Rakova: A. Genetics Department, Hospital Universitario La Paz, IdiPAZ, Madrid, Spain. 8 false negatives were detected in 6 genes (CYP21A2, GLA, GBA, CYP11B1, HBA1/HBA2, ITGB3, VWF). P06.054.C Rare types of the mutations cause pyruvate carboxylase deficiency in 2 patients Polina Tsygankova 1, Nikita Beskorovainiy1, Marina Minzhenkova1, Vyacheslav Tabakov1, Lyudmila Bessonova1, Vera Zarubina2, Natalia Pechatnikova2, Marina Kurkina1, Igor Bychkov1, Ekaterina Zakharova1 1Research centre for medical genetics, Moscow, Russian Federation, 2Morozov Children's City Clinical Hospital, Moscow, Russian Federation. P10.041.A Functional analysis of an RYR1 variant underlying a myopathy with variable expressivity Jennifer Hauteclocque 1,2, Adrien Rihoux3,2, Jean-Denis Brisson4,5,6, Alex Parker1,2, Cam-Tu E. Delon 1, Angus J. Introduction: Pathogenic variants in TBK1 cause amyotrophic lateral sclerosis/frontotemporal dementia spectrum neurodegenerative disorders. Kasubova: None. Conclusion: Our results highlight the

importance of considering alternatively spliced isoforms when calling variants and interpreting their potential functional impact. Methods: We isolated urinary exosomes from 41 SLE patients, 27 with lupus nephritis (LN) and 20 healthy controls, and exosomal miR-146a, quantified by the real-time quantitative polymerase chain reaction (RT-qPCR), was correlated with histological features in 13 renal biopsies. Grants: KR:MR/S004130/1 HomZ = homozygous/compound heterozygous; HetZ = heterozygous; N = number; WML = white matter lesions; ICH = intracerebral haemorrhage; PVS = perivascular spaces. P17.069.D Comparison of methods of genotyping short tandem repeats (STRs) from whole genome sequences John W. Follia: None. nsCPO is a multifactorial disorder with environmental and genetic factors contributing to disease risk. Results: We found 366 (60%) cell lines whose both transcriptomic and epigenomic profiles strongly resemble their cancer type-of-origin. Introduction: Reciprocal translocations occur when part of one chromosome is exchanged with another part of another chromosome. Neither of the patients had survived past three months postnatally. Result: All structural alterations among translocations (e.g., t(1;19), dic(9;12)), aneuploidies (e.g., -7, -11, high hyperdiploidy), and copy number variations (e.g., IKZF1plus profile) known from established techniques were detected by OGM as well. P18.004.B Personalising breast cancer preventionSowmiya Moorthie1,2, Hilary Burton1, Chantal Babb de Villiers 1, Tanya Brigden1, Alison Hall1, Laura Blackburn1, Mark Kroese1 1PHG Foundation, Cambridge, United Kingdom, 2Cambridge Public Health, University of Cambridge, Cambrige, United Kingdom. Using the Human Phenotype Ontology (HPO), we quantitatively dissected the blended phenotype of an infant with severe neurodevelopmental disorder, brain malformation, dysmorphism, and hypotonia. Rodríguez-Girondo: None. Hara-Isono: None. Materials and Methods: We present our comprehensive genetic investigation of 39 patients with syndromic craniosynostosis screened systematically with a combination of cytogenetic analysis, multiplex ligation-dependent probe amplification (MLPA) and array-based comparative genomic hybridisation (aCGH). Zanca: None. Rossokha: None. Conclusions: The main preferences of pregnant women with regard to undergoing invasive prenatal testing and termination of pregnancy in case of detection of a chromosomal abnormality were revealed. To assess their cumulative effects a weighted genetic risk score (wGRS39) was built, and stratified by tertiles. Decreased or lost function of myocardial cells or blood vessels is the cause of coronary heart disease. Performing a targeted reanalysis of those variants, considering only patients whose original WES data was non-diagnostic. Copy-number variation analysis was performed using SNP-array. Stoetzel: None. Conclusions: These findings suggest possible modifier genes to be implicated in NS variable expressivity and phenotype severity, providing new insights in the pathogenesis. Hernández-Maraver2, A. Contribution of following parameters was assessed: specific radiological and orthopedic signs; existence of associated disorders; adult phenotype in familial cases; phenotype of the patient with the same variant from the literature if available, and gene localization of the identified variant. Here, we propose an improved Z-score correlation strategy based on SNPs with low minor allele frequencies (MAFs), and show how this simple strategy can correct the bias generated by the current methods. First, we integrated 24 data sources to develop a standardized collection of 2.4 million regulatory elements in the human genome, transcription factor binding sites, DNase peaks, ultra-conserved non-coding elements, and super-enhancers. We investigated the region using oligonucleotide array Comparative Genomic Hybridization (aCGH). Analysis of whole-exome sequencing data from the AML patients allowed the isolation of clusters of mutant alleles most likely corresponding to different populations of leukemic cells in the sample. Pediatric DCM is a genetic heterogeneous disorder and the yield of the genetic test still remains too low. Freitas: A. Biallelic mutations in Ataxia Telangiectasia Mutated gene (ATM) cause AT phenotype, a disease not well documented in Saudi Arabia, a highly consanguineous society. Automation of library preparation can relieve the burden, but not all liquid handlers are the same, especially when it comes to minimizing errors. Results: Pathological findings were established in 15.3% (6/39) of the cases using aCGH, 8.33% (3/39) using MLPA and 2.85% (1/39) using conventional karyotyping. DNA isolation via the Bionano Prep SP involves measuring 1.5 M cells from bone marrow or peripheral blood, lysing the cells, binding DNA to a paramagnetic disk, washing and eluting the DNA, this process takes 3-4 hours. Anti-tg and anti-TPO antibodies were detected in 3/24 patients (12.5%), anti r-TSH in 2 (8.33%), all in euthyroidism. Servicio de Cardiología., Madrid, Spain, 4Unidad de Insuficiencia Cardiaca y Cardiopatías Familiares. To date, twenty-two individuals have been reported with intragenic ARID2 mutations or deletions at chromosome 12q12-13.11, where ARID2 is located. This work was supported by the Ministry of Health of the Czech Republic (grants AZV 17-30965A, NV19-07-00149, RVO VFN 64165). Over the years, diverse molecular and bioinformatic methods have been used. Yohannes2, Elina Kilpeläinen6, Anastasia Shcherban6, Aarno Palotie6, Katri Kaukinen1, Katri Lindfors1 1Coeliac Disease Research Center, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland, 2Research Programs Unit, Immunobiology, and the Haartman Institute, Department of Molecular Genetics, University of Helsinki, Helsinki, Finland, 3Center for Child Health Research, Tampere University and Tampere University Hospital, Finland, Tampere, Finland, 4Faculty of Social Sciences, Tampere University, Tampere, Finland, 5Laboratory of Computational Biology, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland, 6Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki, Finland. Alesi: None. The most commonly affected gene was PKP2 (12/67 variant-positive cases), followed by KCNH2 (8/67), RYR2 (7/67), TTN (7/67) and SCN5A (6/67). Hearing evaluation and family history were recorded. This work was supported by the Russian Foundation for Basic Research (project 18-29-13045). P12.033.A Cancer Predisposition Syndromes as secondary findings in patients undergoing somatic tumor testing Alexandra Liebmann 1,2, Sorin Armenau-Ebinger1,2, Cristiana Roggia1,2, Stephan Ossowski1,2, Andrea Forschner3, Andreas Hartkopf4, Michael Bitzer5, Yvonne Moeller6, Olaf Riess1,2, Christopher Schroeder1,2 1Institute of Medical Genetics and Applied Genomics, University Hospital Tübingen, Tübingen, Germany, 2Centre for Rare Diseases, University Hospital Tübingen, Tübingen, Germany, 3Department of Dermatology, Center for Dermatooncology, University Hospital Tübingen, Tübingen, Germany, 4Department of Obstetrics and Gynecology, University Hospital Tübingen, Tübingen, Germany, 5Department of Internal Medicine 1, University Hospital Tübingen, Tübingen, Germany, 6Center for Personalised Medicine, University Hospital Tübingen, Tübingen, Germany. Melo3,4,5, Fabiana Ramos6, Lina Ramos6, Jorge M. Background: Kosaki overgrowth syndrome (KOGS) is an ultrarare disorder characterized by characteristic facial features, tall stature, skeletal features, hyperelastic thin skin and MRI brain anomalies. Introduction: Loss-of-function mutations in HINT1 were identified to cause axonal recessive peripheral neuropathy with neuromyotonia (NMAN). Perez-Vazquez: None. Kuschmann: None. Aulchenko1 1Institute of Cytology and Genetics SB RAS, Novosibirsk, Russian Federation, 2Novosibirsk State University, Novosibirsk, Russian Federation, 3PolyKnomics, 's-Hertogenbosch, Netherlands, 4Genos Glycoscience Research Laboratory, Zagreb, Croatia, 5Unit of Animal Genomics, WELBIO, GIGA-R and Faculty of Veterinary Medicine, University of Liège, Liège, Belgium, 6Department of Physiology and Biophysics, Weill Cornell Medicine-Qatar, Doha, Qatar, 7MRC Unit for Lifelong Health & Ageing University College London, London, United Kingdom, 8Colon Cancer Genetics Group, Cancer Research UK Edinburgh Centre, Medical Research Council Institute of Genetics & Molecular Medicine, Western General Hospital, The University of Edinburgh, Edinburgh, United Kingdom, 9Centre for Global Health Research, Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, Edinburgh, United Kingdom, 10Department of Twin Research and Genetic Epidemiology, School of Life Course Sciences, King's College London, London, United Kingdom, 11Department of Molecular Epidemiology, German Institute of Human Nutrition Potsdam- Rehbruecke, Nuthetal, Germany, 12German Center for Diabetes Research (DZD), Neuherberg, Germany, 13Institute of Nutrition Science, University of Potsdam, Potsdam, Germany. P18.038.D Plant extracts as anti inflammatory alternatives at the gene expression level of cytokines AZIZ ALKHADDOUR Southern Federal University, ROSTOV ON DON, Russian Federation. P09.033.B CANVAS: the biallelic RFC1 pentanucleotide repeat expansion in Greek late-onset ataxia patients Zoi Kontogeorgiou 1, Chrisoula Kartanou1, Chrisanthi Tsirligkani1, Evangelos Anagnostou2, Michail Rentzos3, Georgia Karadima1, Georgios Koutsis1 1Neurogenetics Unit, 1st Department of Neurology, Eginitio University Hospital, National and Kapodistrian University of Athens, Athens, Greece, 2Clinical Neurophysiology Unit, 1st Department of Neurology, Eginitio University Hospital, National and Kapodistrian University of Athens, Athens, Greece, 31st Department of Neurology, Eginitio University Hospital, National and Kapodistrian University of Athens, Athens, Greece. C.L. Easter: None. Pathogenic variants were identified in: NPR2 (n = 16), ACAN (n = 11), FGFR3 (n = 8), IHH (n = 8) and SHOX (n = 5). Hinderhofer: None. Two patients displayed a second variant involving a distinct disease. Ziliene: None. Material and Methods: To further elucidate the mechanisms underlying C9ALS/FTD we performed an RNA sequencing study in prefrontral brain cortex samples from 20 C9ALS/FTD and 12 individuals without neurological manifestation and normal C9orf72 repeat alleles. Almstrup: None. Genomic DNA was sequentially subjected to BRCA1/BRCA2 analysis, followed by 25-gene panel targeted sequencing of BRCA1/BRCA2 mutation-negative cases and whole-exome sequencing. Drapkina: None. The splicing patterns of mRNA transcripts were compared by semiquantitative PCR and sequencing. Sobrido: None. M.M. de Jong: None. Conclusions: The inactivation of NOMO1 leads to the differential expression of some genes that could explain its implication in the development of CRC. Introduction: Bi-allelic variants in VARS2, a nuclear gene coding for valyl-tRNA synthetase, cause autosomal recessive combined oxidative phosphorylation deficiency type 20 (MIM#609060), characterized by a variable combination of mitochondrial encephalopathy, developmental delay, hypotonia, epilepsy, cardiomyopathy and structural brain anomalies, usually with a neonatal onset and severe disease course. Brisevac: None. A new syndrome with hypotonia, intellectual disability and eye abnormalities (HIDEA) was recently described in a large consanguineous family from Northern Finland. This work was supported by Research Foundation Flanders (Belgium), Ghent University, German Research Council, National Institutes of Health and Shriners Hospitals for Children. Kozhamkulov1, Ulykbek Kairov1, Gulbanu Akilzhanova2, Ayaulym Chamoieva3, Tolkyn Z. Georgiou4, Christiana A. Racine: None. García-Molina: None. He is the first child of healthy unrelated couple. However, this strategy was not as successful as expected, possibly due to the genetic heterogeneity underlying CRC. F.R. Nitu: None. Notably, there seems to be little knowledge concerning target group needs besides extrapolation from DTC demand. Baldus: None. Introduction: It is now generally accepted that the exact genetic cause of hypertrophic cardiomyopathy (HCM) is unknown in at least 25% of hereditary cases. P17.016.C Cutevariant: a GUI-based desktop application to explore genetics variations sacha schutz Université Brest, Brest, France. Jarno: None. Methods: We analyzed 720 unrelated patients, predominantly of South-Eastern European and Turkish ancestry, with sporadic or recessive CMT who remained unsolved after targeted re-sequencing of the most common CMT genes. The remote counseling raised difficulties which included environmental interferences, problems using the technology modalities, and difficulties involving transferring data. Glotov3, Diana A. Vos1, Rosa L. Cryptorchidism in 3/4. Materials and Methods: The study sample comprised patients with IRD in Iceland ascertained through national centralized genetic and ophthalmological services at Landspitali, a national social support institute, and the Icelandic patient association. T.K. Oleksyk: None. Conclusions: About 10% of patients from our ASD cohort showed rare deleterious variants in multiple genes that seem to fully explain their complex phenotype. Ah Mew: None. Introduction: Zhu-Tokita-Takenouchi-Kim syndrome (ZTTK, OMIM #617140) is a recently described multisystemic disorder caused by de novo heterozygous pathogenic variants in SON gene. There was no statistically significant difference of DNA methylation level of the MLH1 promoter region (GRCh37/hg19; chr3:37,033,249-37,033,762) between groups of patients and healthy individuals, although the mean methylation levels for individual CpG-sites varied significantly (from 0.1 to 12%). Castillo-Fernandez: None. WGBS revealed 71 significantly differentially methylated regions between high and low altitude Tibetans (FDR 15%. P01.068.D Structural fetal defects after preimplantation genetic testing - high throughput genetic investigations Radostina Raynova 1,2, Petya Chaveeva2, Tanya Milachich2, Momchil Rizov2, Tanya Timeva2, Atanas Shterev2, Ivanka Dimova2,3 1National Genetic Laboratory, Sofia, Bulgaria, 2SAGBAL"Shterev", Sofia, Bulgaria, 3Medical University, Sofia, Bulgaria. Therefore, detection of hereditary genetic variations associated with prostate cancer progression and outcome has a significant impact on the accurate classification of the disease, providing insight into possible preventive and therapeutic targets. Langlet: None. Interestingly, the c.3402del variant has also been reported as the most frequent in WD cohorts from Venezuela and Brazil. Conclusion: Microarray-based comparative Genomic Hybridization (aCGH) is essential for evaluating derivative chromosomes of unknown origin. In compound heterozygous state with typical loss-of-function mutation it causes adult onset form of NPC. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Significant; Medical Research Council, National Institute for Health Research. E.T. Dermitzakis: F. P.D. Lambiase: None. The distribution of genotype frequencies of COL1A1 rs1800012 variant in the cases significantly differed from the CON (GG/GT/TT: 44/32/24% vs 89/10/1%; p T;p.(Gln128Ter) to determine the frequency of this variant in the fertile male population. Introduction: High-grade serous ovarian cancer (HGSOC) is the most common histological subtype of epithelial ovarian cancer, with a five-year survival rate below 30%. H.T. Bjornsson: None. Although general values and trust both played key roles in participation, potential withdrawal, and willingness to permit data linkage, they were differentially associated with motives for participation and withdrawal. However, these alterations remain underestimated. Alfieri: None. J.M. Piulats: None. Results: A clear paternal age effect was observed, with 70 DNMs detected on average in children born to young fathers and 94 DNMs in those born to older fathers (p = 0.001). Introduction: HPV infection leads to imbalance in pro-and anti-inflammatory cytokines which promotes for long-term persistence of the virus in the infected cells. J.L.F. Fung: None. Oruganti: None. P24.047.B A data-driven review of the genetic factors of pregnancy complicationsYury Barbitoff1, Alexander Tsarev2, Elena Vashukova1, Evgeniia Maksiutenko3, Ludmila Kovalenko4, Larisa Belotserkovtseva4, Andrey Glotov 1 1Ott's Institute of Obstetrics, Gynaecology and reproductology, St.-Petersburg, Russian Federation, 2Bioinformatics Institute, St.-Petersburg, Russian Federation, 3St. Petersburg State University, St.-Petersburg, Russian Federation, 4Surgut State University, Surgut, Russian Federation. The fourth was 64 years and present dimorphic features. Diquigiovanni: None. Rotter: None. Mihailescu: None. Thus, APOBEC mutagenesis has a high propensity to generate impactful, gene-altering mutations, exceeding other well known carcinogens such as tobacco smoking and UV-light. Meta-module protein abundance is reduced whilst proteins mediating focal adhesion and cytoskeletal dynamics are increased in OA. Varga: None. A highly recurrent HLRCC-associated missense variant [FH: c.1118A>G; p.(Asn373Ser)] was observed in apparently unrelated families from the southeast of Spain. Romani: None. Hommam: None. A.S. van der Werf-'t Lam: B. To confirm an endogenous enhancer activity, we develop CRISPR interference (CRISPRi), new approach for targeted silencing of transcription in human cells. Molecular data: variants were identified by exome sequencing; all of them were protein truncating variants: 4 nonsense, 4frameshift and one affecting a splice-donor site; 2/9 previously described. Rannikmae: None. These survey results suggest that efforts to collect and share genomic data should consider and adapt to the social distribution of trust and willingness to share in the population, and that further research should explore the specific social and cultural contexts of genomic data. Extensive genetic testing including whole-exome and whole-genome sequencing (short-read) were inconclusive. Besides facial dysmorphism, he had bilateral syndactyly. Melanoma samples were analyzed by NGS with a custom hybridization-capture based sequencing approach investigating approximately 150 genes recurrently altered in various malignant neoplasms. Oleksyk3, Volodymyr Smolanka2 1Oakland University, Rochester, MI, USA, 2Uzhhorod National University, Uzhhorod, Ukraine, 3A. P.I. Sergouniotis: None. Posteriorly, the sequencing of the RBM8A gene revealed the pathogenic variant c.-21G> A, in hemizygosis, confirming the diagnosis of TAR syndrome. The baby was born at 36 weeks of pregnancy weighing 2930 g, length 49 cm, on the Apgar scale 8/8 points. Weiss: None. Here, we aimed to map and functionally study CREs of the abca4 region and generate a stable knock-out of a CRE of abca4 in X. Conclusions: We proof analytical and clinical validity of our liquid biopsy assays to determine recurrence and progression in CRC. Network analysis highlighted non-random interconnectivity between the genetic modifiers identified in DMD patients, and potentially shed light on new genetic modifiers by their functional coupling to these known genes. Speakers Bureau/Honoraria (speakers bureau, symposia, and expert witness); Modest; Novartis, Sanofi Genzyme, Almirall, TEVA, Merck-Serono. Z.C. Akdemir: None. The patient constitutional karyotype was: 46, XX; t(5;22)(q35.1;q11.2). Introduction: Developing precision public health and personalised prevention is an ambition for many health systems as evidenced by government policy documents. Lapucci: None. L.J. Howe: None. Rozemuller2 1Pacific Biosciences, Menlo Park, CA, USA, 2GenDx, Utrecht, Netherlands. Guirado: None. Introduction: Knowledge on the experience of families where a child has Down syndrome (DS) is essential to genetic counselling and family support. Hoefsloot, Andre G. R.S. Møller: None. In Xq27.3, the breakpoint is situated in an intergenic region. P04.067.D Atypical type VI Osteogenesis Imperfecta mouse models the intersection of IFITM5 and SERPINF1 pathways in patients Gali Guterman Ram 1, Ghazal Hedjazi2, Chris Stephan3, Stéphane Blouin2, Victoria Schemenz4, Wolfgang Wagermaier4, Jochen Zwerina2, Peter Fratzl4, Kenneth M. Genotyping was performed using Illumina Infinium® HD SNP arrays. Ryan: None. Graça Velon: None. RA is considered as a multifactorial disease triggered by a genetic predisposition and environmental factors. Limborska1, Lyudmila V. Tõnisson: None. Lench1, Louisa Ive1, Eva Serra1, Natalie Trump1, Nayana Lahiri2, Janna Kenny2, Frances Elmslie2, Phil Ostrowski2, Esther Dempsey2, John Short2, Charlene Crosby2, Christine M. Slightly higher diagnostic yield was observed associated with severe (OFC more than 3 SD below the mean), 26.42%, than mild microcephaly, 20.45%. Previously, such traits were annotated with multiple EFO terms in the same field (i.e. allergic rhinitis, asthma). BACKGROUND: Malignant pleural mesothelioma (MPM) is a rare and aggressive neoplasm strongly associated with asbestos exposure. Polishchuk: None. SNPs were assigned to genes via positional mapping (distance GH (heavy strand notation) substitutions in mtDNA is positively correlated with cellular and organismal longevity (. Coelho: None. Therefore, in this study, we investigate the causal relationship between SNPs associated with circulating CRP-levels and the risk and severity of acute appendicitis. Vuletic: None. Mesnard: None. Finally, the relationship between WTS and religiosity is complex; while religious people seem less inclined (58%) than non-religious (62%) towards sharing with "My Medical Doctor" this trend is overturned when considering sharing with "For Profit Researcher" (religious 41% vs non religious 32%). Funding was from the GOSH NIHR Biomedical Research Centre. Salomon: None. After the expulsion, fetuses were either immediately autopsied or preserved overnight at 4ºC and transferred to the Pathology Department within maximum 12 hours. Scheidecker: None. Primers' system for Sanger sequencing was designed and validated for coding 2-12 exons of ALPL gene. García: None. P.A.C. 't Hoen: None. Zastavna: None. Presenting a large family with Lynch syndrome and FBX011-related intellectual developmental disorder Malene Lundsgaard 1, Uffe B. Three SNPs presented significant values in neutrophil count and in gamma chains ratio. S.A. Paracha: None. Studies in a heterozygous knock-in mice-model have shown 60-80% striatal dopamine reduction as a result of the dominant-negative effect of mutant alleles. Birk3,1 1The Morris Kahn Laboratory of Human Genetics, National Institute of Biotechnology in the Negev, Beer Sheva, Israel, 2Department of Ophthalmology, Soroka Medical Center, Beer Sheva, Israel, 3Genetics Institute, Soroka Medical Center, Beer Sheva, Israel. *These authors contributed equally. Servicio de Análisis Clínicos. Conclusions: If ranged, CFTR variants spectrum from regional CF cases resembles that of common Russian alleles for 5 major variants (except R1066C, listed in Table), while sharing only 2 major mutations with Europe ([delta]F508, N1303K). P24.005.D Harnessing tissue-specific genetic variation to dissect the causal pathways between adiposity and complex disease Genevieve Leyden, Chin Yang Shapland, George Davey Smith, Michael Greenwood, David Murphy, Tom G. We have successfully detected known pathogenic variants across different cell lines using as few as 2,500 cells, providing a path forward to achieving the full potential of WGS inclinical scenarios where samples are small, rare, and irreplaceable. Behind the Seizure® (BTS) is a US-based, sponsored testing program for children with suspected genetic epilepsy, initiated with the goal to help lower the age of CLN2 disease diagnosis. Methods: We evaluated 156 young patients diagnosed with sarcoma for the presence of germline variants using a custom 113 gene panel and Next-Generation Sequencing (NGS). 3) Applying custom virtual gene panels required trained bioinformaticians. WES of 197 samples shows an non-reference concordance of 95% for singletons. We will prospectively recruit and analyze additional patients to identify new disease-relevant genes. Within the associated region, a BMP3 coding variant was prioritized as the candidate causal variant, alongside non-coding potentially regulatory variants. Intronic pathogenic deletion c.925+20_926-48del101was found in two brothers in compound heterozygous state. Cleton-Jansen: None. Williams5, EARGEN consortium 1Karolinska Institutet, Stockholm, Sweden, 2Erasmus Medical Center, Rotterdam, Netherlands, 3King's College, London, United Kingdom, 4Nottingham University, Nottingham, United Kingdom, 5King's College, London, United Kingdom. Lanos: A. Co-occurring MLH1 promotor hypermethylation and MMR germline mutation cases are rare but do exist. The duplication was absent in DNA from the parents. Hospital General Universitario Gregorio Marañón, Madrid, Spain, 45Institut für Humagenetik, Universitätsklinikum Essen, Essen, Germany, 5Institüt für Humangenetik, Universitätsklinikum Düsseldorf, Düsseldorf, Germany, 6Servicio de Cardiología. The overall prevalence of severe HPP is range from 1/100 000 to 1/300 000. Sukys: None. Kuzu: None. P02.002.C Genetic and environmental factors influencing sensory decays during aging in a large Italian cohort Giorgia Girotto 1, Massimiliano Cocca2, Anna Morgan2, Eulalia Catamo2, Paola Tesolin1, Agnese Feresin1, Paolo Gasparini1, Maria Pina Concas2 1University of Trieste-IRCCS-Burlo Garofolo, Trieste, Italy, 2IRCCS-Burlo Garofolo, Trieste, Italy. Here we provide a definition for cytogenomics, which has a comprehensive and integrative view. Nauth: None. b. Delayed diagnosis and late introduction of appropriate management are common. This situation underlie the need for better understanding of this phenomenon during PGT-M management to prevent reduction of reproductive chance of patients coping with such tedious treatment procedures. The autophagy markers LAMP1 and LC3β showed reduced expression in patient derived fibroblasts in line with MS results. Conclusions: We described the largest NF1-deleted cohort to date and confirmed a more severe phenotype in NF1-deleted patients with a predominant maternal origin of the deletions. Sommer 1, Iris B. Manase: None. He could understand spoken language but could not speak. Hilger: None. Ugenskienė: None. In addition, it illustrates the importance of cytogenetics in the diagnosis of this disorder. The importance of cytogenetic and FISH in Hematology Filipa Seixas, Pedro Sousa, Regina Arantes, Marta Souto, Patricia Ferraz, Osvaldo Moutinho, Manuel Cunha, Rosário Pinto Leite Centro Hospitalar Trás os Montes e Alto Douro, Vila Real, Portugal. Results: IRAK2 rs3844283 C allele was detected in 66% of RA patients and 74% of controls. K.M. Kozloff: None. Lastly, interaction analysis was performed to better characterize the MPM OR. We reported previously that Ppib-/- mice have abnormal type I collagen post-translational modification and crosslinks. Introduction: Usher syndrome (USH) is the most common cause of combined sight and hearing loss, responsible for half of deaf-blindness cases. Peña-Guerra2, Yolande van Bever1, Barbara W. Acknowledgement: BSNF, Contract NoКП-06-H33/10, 2019. At last follow up she showed drug resistant epilepsy with daily seizures, cognitive, motor, and severe language deficits and behavioural disturbances.NGS analysis did not reveal pathogenic variants in genes associated with epileptic encephalopathies. One further patient with café-au-lait spots, epilepsy, developmental and psychomotor delay, harbored two NF1 variants: a heterozygous variant c.731-2A>C co-segregating with NF1 in affected relatives, and a deletion of exon 19. Orofacial clefts (OFCs) are among the most common human birth defects. GRS explained less variation in alcohol consumption among participants whose alcohol consumption fall in the centre of the population distribution of alcohol consumption and explained more variation in participants with higher alcohol consumption. The SNP heritability is 16.36% (P = 0.16). Amelina: None. Upon targeted sequencing, we identified 6 carriers of pathogenic alleles in NBN (n = 3), ATM (n = 1), PALB2 (n = 1), and RAD51D (n = 1) genes. This study was supported by KTIA_13_NAP-A-III/6; KTIA_NAP and with the FIKP program T. Outcomes: Clinical geneticists can remotely review neonates and provide support promptly and efficiently. Each manipulation with live SARS-CoV (Urbani, Erasmus University Medical Center, Rotterdam) and SARS-CoV-2 (nCoV/Victoria/1/2020) viruses was performed under BSL-3 conditions. A further paternally inherited variant affected CPLX3, involved in neurotransmitter release, hypothesized to be implicated in neurodevelopmental delay. The developed approach can also be used to identify genotypes and epigenotypes characteristic of the development of other multifactorial conditions and polygenic diseases. B.C. Widemann: None. Pellegrinelli: A. Variants of BRCA1 (rs80357713, rs80357711, and rs80357906) and BRCA2 (rs80359550) were detected using a custom panel. She was treated with low-fat diet, insulin, fibrates, omega-3 fatty-acids and several sessions of apheresis during pancreatitis episodes. Conclusions: The PIEZO1 variant presents as an important candidate for the cause of the hydrops fetalis in an autosomal recessive manner in this Cypriot family. We aimed to test the potential causal role of TL in age- and AD-related brain structure alterations through a Mendelian Randomization (MR) analysis. c.933+3A>C p? Mazzeu2, Hubertus J. Also, interesting cases with variants in SYNE1 or ALS2 highlight the wide phenotypic spectrum associated with HSP. Material and method: 2307 patients who benefited from a telemedicine consultation by telephone or videoconference between March and December 2020 from the five genetic consultations of the east of France were asked by e-mail or by post to answer an online satisfaction questionnaire. The 3D structure of the mutant protein was predicted computationally. Additionally, our preliminary data shows substantial impact on job satisfaction. Lezheiko: None. Method: The CARTaGENE database regroups individuals between 40-69 years old with no known neurodegenerative disease. The reasons for referral were developmental delay, fetus with multiple congenital abnormalities at ultrasound, critically ill children from intensive care unit, cardiomyopathy, hereditary cancer, epilepsy, and skin abnormalities. Employment (full or part-time); Significant; GeneDx. P.M. Krawitz: None. Sena AYDOS 1, Dunya AYDOS2, Yunus YUKSELTEN3, Asuman SUNGUROGLU1, Kaan AYDOS4 1Department of Medical Biology, Ankara University School of Medicine, Ankara, Turkey, 2Ankara University Stem Cell Institute, Ankara, Turkey, 3Research Laboratories for Health Science, Y Gen Biotechnology Company Ltd., Ankara, Turkey, 4Department of Urology, Ankara University School of Medicine, Ankara, Turkey. I. Scansetti", University of Turin, Turin, Italy, 13Medical Genetics Unit, AOU Città della Salute e della Scienza, Turin, Italy. Patient 3 showed a terminal deletion of 22q13.33 region, including the gene SHANK3. Kaygısız: None. C.D.M. van Karnebeek: None. Ibáñez-Mico: None. Transcriptome analysis performed formalin-fixed paraffin-embedded (FFPE) of testicular tissue revealed the loss of expression of several genes and microRNAs associated to cell proliferation signaling pathways. Schouten1, H. Moresco: None. Paynton4, Luis A. Results: We have identified inherited damaging variants in Cav3 genes in 21 ASD families. Physical examination showed short stature and facial dysmorphisms including mild frontal bossing, midface retraction, low-set-ears, downslanting palpebral fissures, broad and depressed nasal bridge, full cheeks, short philtrum, small mouth and micrognatia. Köttgen: None. Yilmaz1, Selim Buyukkurt2 1Faculty of Medicine, Dept of Medical Biology, Adana, Turkey, 2Faculty of Medicine, Dept of Obstetrics and Gynecology, Adana, Turkey. Shaviv: None. Christou: None. P05.012.B OBSCN as a candidate gene for apical hypertrophic cardiomyopathy Busra Unal 1,2, Nihat Bugra Agaoglu1,2, Ozlem Akgun Dogan3,2, Levent Doganay1,2,4, Mehmet Agirbasli5 1Department of Clinical Genetics, Umraniye Teaching and Research Hospital, University of Health Sciences, Istanbul, Turkey, 2GLAB (Genomic Laboratory), Health Directorate of Istanbul, İstanbul, Turkey, 3Department of Pediatric Genetics, Umraniye Teaching and Research Hospital, University of Health Sciences, Istanbul, Turkey, 4Department of Gastroenterology and Hepatology, Umraniye Teaching and Research Hospital, University of Health Sciences, İstanbul, Turkey, 5Department of Cardiology, Goztepe Teaching and Research Hospital, Istanbul Medeniyet University, Istanbul, Turkey. B.W. van Paassen: None. Stratis: None. Patients and Methods: Thirty-five HED patients descending from 32 unrelated pedigrees were clinically diagnosed based on thorough clinical and dental examination. Desbats: None. The parent's karyotypes were normal. Consultant/Advisory Board; Modest; Janssen, Takeda. Ryten: None. Ruzanova1, Elena M. We did chromosomal analysis followed by exome sequencing for the living proband and her parents. J.M. Wierzba: None. Patel1 1University of Exeter Medical School, Exeter, United Kingdom, 2Royal Devon & Exeter NHS foundation trust, Exeter, United Kingdom. Objectives: We investigated the genetics of the plaque through multivariate and integrative genome-wide analyses (GWAS) of individual plaque characteristics. Results: Genetic variants could be identified in 29 (52.7%) of the 55 studied non-syndromic ARCI families. We could, however, not reject population continuity, which is relevant to future (paleo)epidemiological and selection studies in the datasets presented here. Ros: None. H.K. Zieger: None. Conclusion: Our patient may have a KBG (MIM 148050) overlapping phenotype. Post-translational modifications are predicted to be critical for several main components at the NMJ. HD Hub is a web-based platform that provides interactive and real-time visualizations and analysis of HDL results. P17.007.B Software assessment for prioritization of germline causal variants of disease from whole-exome sequencing data Eva Tosco-Herrera 1, Alejandro Mendoza-Alvarez1, Hector Rodriguez-Perez1, Adrian Muñoz-Barrera2, Antonio Iñigo-Campos2, Almudena Corrales1,3, Francisco Martinez Bugallo4, Carol Prieto Morin4, Rafaela González-Montelongo2, Jose Miguel Lorenzo-Salazar2, Carlos Flores1,2,3, Laura Ciuffreda1, Itahisa Marcelino-Rodriguez1,5 1Research Unit, Hospital Universitario Nuestra Señora de la Candelaria, Santa Cruz de Tenerife, Spain, 2Genomics Division, Instituto Tecnológico y de Energías Renovables (ITER), Santa Cruz de Tenerife, Spain, 3CIBER de Enfermedades Respiratorias, Madrid, Spain, 4Clinical Analysis Service, Hospital Universitario Nuestra Señora de la Candelaria, Santa Cruz de Tenerife, Spain, 5Instituto de Tecnologías Biomédicas (ITB), Universidad de La Laguna, Santa Cruz de Tenerife, Spain. Liang: None. Acknowledgement: This study is funded by the Research Grant (RAC#2110006, 2180031 to DC). Moles-Fernández: None. Results: Through NGS in FH probands, we identified new PCSK9 rare variants: p.(Arg215Cys), p.(Asp367His), p.(Glu410Lys), p.(Arg495Trp), p.(Gly516Val), p.(Ala676Gly), all are predicted deleterious, but functional studies are needed to establish their real causative effect. Giangiobbe: None. Doddato: None. WGS offers a more comprehensive genetic workup for severe primary or idiopathic PIPO because of such genetic heterogeneity. Zhu: None. The aim of MobiDetails is to gather in a single web page for each variant the most significant data, with a particular focus on splicing prediction tools. Reboul: None. M.D. Metodiev: None. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Modest; Sanofi. P23.040.D The psychosocial experience of families with hereditary amyloid transthyretin amyloidosis with polyneuropathy: a mixed-methods systematic review José D. Vetchinkina1, Alexey I. The histopathological analysis of the abdominal aortic wall was carried out. Due to this complex phenotype, whole exome sequencing was performed by Sure-SelectXT Human All Exon V5 (Agilent Technologies, USA). The study was partially founded by CMHI grant S177/2018. P12.142.B Next generation sequencing for germline mutation analysis in patients with neurofibromatosis Daniela Pencheva, Kunka Kamenarova, Kalina Mihova, Ivanka Dimova, Vanio Mitev, Radka Kaneva Molecular medicine center, MU- Sofia, Sofia, Bulgaria. A.O. Smirnova: None. Dong: None. Here, we aim to better characterize SHS phenotype. University Hospital Schleswig-Holstein, Lübeck, Germany, 13Department of Pediatrics, College of Medicine, Qassim University, Riyadh, Saudi Arabia, 14Division of Genetics, Department of Pediatrics, King Abdullah Specialized Children Hospital, King Abdulaziz Medical City, MNGHA, Riyadh, Saudi Arabia, 15Department of Genetics, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia, 16John Hopkins Aramco Health Care, Pediatric Services, Dharan, Saudi Arabia, 17University of Rostock, Rostock, Germany. Conclusion: We created and successfully tested a minigene expression system for assess the effect of variants in PAX6 gene on pre-mRNA splicing. Hawlina: None. We selected for follow-up 11 regions (23 genes), that showed the highest ranking in a meta-analysis performed in large Italian sample sets. This approach allows the user to visually inspect the output to further reduce the false positive rate. Oselin: None. Nigro: None. F.J. Guzmán-Vega: None. The small format and convenient workflow, with the lack of instrumentation, allows PIPseq to be easily implemented in high-containment laboratories. Methods: We report here the clinical and molecular characterization of 5 unrelated patients, 4 with loss-of-function WAC variants and 1 with a deletion encompassing 10p11.23. Four microdeletions were considered suggestive for well-delineated single-gene syndromes, namely Nance-Horan(NHS),Phelan-McDermid(PMS),Hand-Foot-Genital(HFGS),and Feingold Type2(FS2).The first microdeletion,harbored the NHS along with 21 other genes in Xp22.2p22.13(16051468_18313707)(GRCh37/hg19).The boy had microphthalmia/cataract,mild global developmental delay,ventricular septal defect which was well overlapped with the clinical findings of NHS. We demonstrate that lymphatic pathology including PLE, lymphatic malformation and lymphedema can be a part of both conditions. Arrate Pereda 1, Yerai Vado1,2, Karen E. We achieve this by leveraging Natural Language Processing (NLP) to infer both disease-relevant annotation terms and known disease-associated gene lists. H.A.A. Radwan: None. Aim: Von Willebrand disease (VWD) is the most common inherited bleeding disorder caused by pathogenic variants in VWF gene. P24.044.C Omingenic model of control of N-glycosylation of immunoglobulin GArina Nostaeva1, Sodbo Sharapov2, Gordan Lauc3, Michel Georges4, Yury Aulchenko 2 1Novosibirsk State University, Novosibirsk, Russian Federation, 2Institute of Cytology & Genetics SD RAS, Novosibirsk, Russian Federation, 3Genos Glycoscience, Zagreb, Croatia, 4GIGA Institute, University of Liege, Liege, Belgium. Conclusions: Putative cerebellar and SH-SY5Y enhancer regions are quite similar for three of the four SCA genes now tested. Möslein: None. Introduction: Primary coenzyme Q10 deficiency (primary COQ10 deficiency) is a mitochondrial respiratory chain disease caused by biallelic variants in: COQ2, COQ4, COQ6, COQ7, COQ8A, COQ8B, COQ9, PDSS1 or PDSS2. Brain magnetic resonance image (MRI) showed mild hyperintense gliotic signals compatible with mild hypoxic ischemic sequelae. Materials and Methods: The 2-step long-range PCR was developed for the amplification of CYP2D6 locus and applied to 22 samples from a pharmacogenomics reference panel. P10.026.B A family with mutation in DMD that inherited from gonadal mosaic mother Basak Gogus, Muhsin Elmas Afyonkarahisar Health Science University, Afyonkarahisar, Turkey. Witters: None. Elbracht: None. Plasmid with NUDT16L1 CDS under CMV promoter was used for NUDT16L1 overexpression. Conclusions: Urinary exosomal miR-146a levels are correlated with lupus activity, proteinuria and histological features, discriminating patients with LN and being a good baseline marker of SLE flares. A relative increase in miR-625-3p expression after treatment for more than 3.2% was associated with much shorter progression-free survival (7.5 vs 19.4 months, P = 0.024) and overall survival (12.5 vs 49.1 months, P = 0.043) of MM patients. Here, we aim to characterize, at the level of mutations and transcriptomics, the tissue-specific patterns of two key players in the cancer initiation – activation of oncogenes and inactivation of tumor suppressors (TS). Because of the clinical findings of our patients, the evolutional conservation of p.Leu6267 and the co-segregation of the variant, we identify the novel c.18800T>C, p.(Leu6267Pro) variant as disease causing. Further credible novel variants have also been recently identified in genome wide association studies. Olivieri: None. Segregation analysis was performed using Sanger sequencing. Auditory neuropathy represents 5-10% of child's hearing loss. Jehee1, Marieke Joosten1, Marjan Boter1, Walter de Valk1, Robert van der Helm1, Erik Sistermans2, Els Voorhoeve2, Shama Bhola2, Mariette Hoffer3, Nicolette den Hollander3, Merryn Macville4, Diane Van Opstal1 1Erasmus MC, Clinical Genetics, Rotterdam, Netherlands, 2Amsterdam UMC, Vrije Universiteit Amsterdam, Clinical Genetics, Amsterdam, Netherlands, 3Leiden University Medical Center, Clinical Genetics, Leiden, Netherlands, 4Clinical Genetics, GROW School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, Netherlands. We describe the genomic and phenotypic findings of SD cases referred to clinical genetics over an approximately 2.5-year period. The allele frequencies from the GnomAD base for Caucasian were used as control. Phenotypic features of 17p13.3 microduplication-syndrome (MIM #613275) include developmental and psychomotor delay, behavioral problems, distinct physical features, postnatal-overgrowth and ASD, as well as limb malformations and cleft lip and palate. However, when isolated, abnormal CMA rate is only slightly higher than the background risk. Further investigation (GWAS replication combined with in vivo studies in animal models) are needed to confirm our results that will ultimately help to understand better the complex biological mechanisms underlying MIS and ageing. Palmal: None. Results: In 8/27 (29,6%) PC patients 9 variants of analyzed genes were detected. Carreño: None. Coriat: None. Patients with normal or inconclusive results were analyzed with microarray. TTR circulates primarily as a 55 KDa tetramer. Vierlinger: None. The median number of CAG repeats for the mutant allele is 46 repeats. Ruivenkamp12, Daniela Q. A limitation of genome-wide PRS is the condensation of biologically distinct mechanisms and differing effect directions. Grisval: None. Kortüm: None. This case demonstrates the need for careful evaluation of pregnancies in which mosaic embryos are transferred; with emphasize on the use of high- throughout whole genome techniques for copy number analysis. Materials and Methods: We present a 13-year-old boy with typical craniofacial characteristics (coarse facial features, highly arched eyebrows, widely spaced eyes, prominent nasal bridge, wide mouth, retrognatia, dysplastic ears, skeletal abnormalities) and mild intellectual disability. Introduction: Observational evidence suggest that physical inactivity leads to weight gain, but some studies indicate reverse causality where weight gain leads to inactivity. Reduction of mutant protein could be recovered by treating the cells with cycloheximide and MG132. Our patient's severe phenotype is due to the concomitant loss of function of SCN1A and SCN2A.This new technology allowed a proper characterization of the rearrangement, defining a better molecular diagnosis that leads to precise treatments and clinical outcome. This research is supported by ERN-ITHACA. Keren: None. Numerical changes and translocations were also observed. This resource provides statistics on natural selection as the absolute scores and rank scores representing −log10(P-value) at 0.01 FDR for the SNP compared to others in the whole-genome context. M.A. Loizidou: None. Materials and Methods: A 39 y.o. woman was referred for a peripheric neuropathy, sensory deficits and distal-predominant weakness. Multiple cavernous malformation were observed on his brain tomography. The functional relationship between L1CAM and KIF4A supports this evidence, but the mechanism needs to be further elucidated. For our in-house samples, we performed benchmarking on reportedly (likely) pathogenic HGMD/ClinVar variants, enabling performance assessment for sequence variants with potential clinical relevance. References: 1. Korobeinikova: None. Hahn: None. Chwialkowska: None. Dr. İlhan Varank Training and Research Hospital, İstanbul, Turkey. SCRIB gene role in spermatogenic failure has not been reported. Mudun: None. Tasic: None. This case could expand the clinical spectrum of 16p12.2 patients. Introduction: GUCY2D gene encodes the photoreceptor guanylate cyclase (GC-E) and different mutations can lead to cone-rod dystrophy (CRD), congenital stationary night blindness (CSNB), and Leber congenital amaurosis. Blasio: None. ENMG showed a marked neurogenic involvement. Results: One-year later genetically-instrumented ANM increased the odds of female-specific hormone-sensitive cancers by up to 5%. Therefore, a severe constitutional PP deficiency caused by de novo POLE variants, which may have a stronger "mutator" effect than POLE/D1 PV causing PPAP, should be considered as a differential diagnosis to CMMRD. L.D. Howe: B. Markov1, Ekaterina S. This disorder was recently reported, and evidence suggests a positive response to treatment with oral uridine. Data can be requested for a single gene or in batches through an R query. Taylor: None. Giacalone: None. Alsubhi: None. Capristo: None. The filtering of variants is also often focused on coding parts, leaving out functionally relevant intronic variants. Both global and regional sex-specific heritabilities were estimated using LD-score regression and Heritability Estimation from Summary Statistics (HESS). P04.009.B Defining the molecular pathology of autosomal recessive congenital icthyosis among a cohort of Egyptian patientsKhalda S. All the cases showed dysmorphic feature, but not suspected as KMS until they visited genetic clinics. Employment (full or part-time); Significant; The Department of Molecular and Human Genetics at Baylor College of Medicine derives revenue from molecular genetic testing offered at Baylor Genetics.. Ternadi: A. Timms: None. P12.183.C Exome sequencing identified potential causative candidate genes for serrated polyposis syndrome Sophia Peters 1, Anna K. Furthermore, we found high correlation (>0.9) of methylation frequencies compared to bisulphite and high reproducibility between runs on a per base level as well as for larger features like CpG islands. P04.068.A Study of OI patient osteoblasts to investigate phenotypic variability of dominant osteogenesis imperfecta Milena Jovanovic, Apratim Mitra, Ryan Dale, Joan Marini NICHD/NIH, Bethesda, MD, USA. They are currently under revision (to be adopted by the end of first semester 2021). Pujol: None. Bruel: None. Andújar: None. Decrease of HDR due to NUDT16L1 overexpression gives new information about the protein, and can be used in further studies of NUDT16L1. While most of the common variation is shared with other European populations, this survey of population variation contributes a number of novel SNPs and structural variants that have not been reported in the gnomAD/1KG databases representing global distribution of genomic variation. Moosajee: None. Acknowledgment: KP-06-N33/5 from 13.12.2019 - National Science Fund of Bulgaria. Conclusions: While our findings suggest that genetic factors contribute to transdiagnostic symptom dimensions in MDD, BD, SCZ, and SZA and thus indicate shared etiological factors, no replicable genome-wide associations could be identified at the given sample sizes. Genetic counselling, in contrast, involves not only complex information often surpassing the patient's knowledge on health and disease, but also value-laden questions such as parent-offspring disease transmission, pregnancy fate after prenatal diagnosis, genetic testing in late-onset disorders, uncertain prognosis. Abbondanza: None. The IKBKG gene partial deletion or intragenic mutations were investigated by a long-range PCR, multiplex ligation-dependent probe amplification, and direct sequencing methods. It is caused by pathogenic germline variants in AXIN2 gene. Haworth: A. Veleva: None. 582 nodes and 2102 edges were mapped in the PPI network of identified DEGs, including 388 up-regulated and 1318 down-regulated genes. Most consumers are satisfied with DTC-GT and trust their results, but do not complete as many post-test actions (sharing results, accessing healthcare, and changing behaviours) as they intended to. The right hemisphere was sliced and samples were preserved in 4% paraformaldehyde for ultrastructural studies or snap-frozen at -80ºC, for omic studies, immunohistochemistry analysis or preserved for future research. Results: We assessed the expression levels of miR-195-5p and miR-195-3p between the ADC and adjacent normal tissues and found expression of miR-195-3p to be significantly differentially downregulated (p A (p.I51N), inherited from her mother, and c.602G>A (p.R201H), inherited from her father, was detected. We studied a girl presenting with isolated high myopia. Upon informed consent, genomic DNA was isolated from peripheral blood samples and analysis of ASS1 was carried out. CNV analysis enabled finding causative variants for additional 9 patients (51% overall), however, CNV identification performed sub-optimal in several batches due to technical bias and a low number of samples per pool. The 22q11.2 microduplication syndrome shows highly variable phenotypes with reduced penetrance. Lucassen1 1University of Southampton, Southampton, United Kingdom, 2Cardiff University, Cardiff, United Kingdom. Perpiñán: None. Beniusyte: None. Results: 61 patients with HCM: 15 Pathogenic or likely pathogenic variants (25%) and only 9 VUS were considered with high probability of pathogenicity (15%). Methods: We report 11-years old boy who was referred to geneticist due to suspected hereditary ataxia. Di Nardo: None. To characterize the effect of these variants at mRNA level the minigene assay was performed. P02.049.B Genotype phenotype correlations of 37 DFNB9 patients with auditory neuropathy and 17 new OTOF pathogenic variantsSophie Achard1, Margaux SEREY-GAUT2, Laurence Jonard 3, Isabelle Rouillon1, Marine Parodi1, Natalie Loundon1, Elisa Rubinato2, Sandrine Marlin2 1Hopital Necker - Service d'ORL, Paris, France, 2Hopital Necker - Service de Génétique Clinique, Paris, France, 3Hopital Necker - Service de Génétique Moléculaire, Paris, France. Bouvignies: None. Methods: Family and cohort studies were performed and included exome sequencing and characterization of hearing phenotype. E.R. Woodward: None. Kolvenbach1,2,3, Tim Felger2, Luca Schierbaum1,3, Isabelle Thiffault4, Thomas Smol5, Allan Bayat6, Frederic Thieme3, Kerstin U. Rodríguez-Nóvoa: None. Zaanan: None. N.V.A.M. Knoers: None. However, cerebral, spinal and lower limb abnormalities haven't been described in DASS. Camarena: None. Frequencies differ notably between ethnic groups. Results: We have found a significant burden of ultrarare SV variants in severe tinnitus patients when compared with Swedish controls ((SV)=pvalues: (DUP)=1,2e-08; (DEL)=9,4e-04; (INS)=4,1e-12). Almost the same shaping shown after UVB treatment, but STAT4 elevated in 57% of patients. Conclusions: Transparent and coherent variant-/genotype-interpretation enables physicians to diagnose hereditary diseases and allows them to provide patients with well-founded information concerning prognosis and recurrence risk. This variant is located in a canonical donor splice site, suggesting a possible alteration of the splicing process and a loss of protein function. Papagregoriou: None. Gene set enrichment analysis (GSEA) was performed to identify the biological pathways associated with the expressed genes. Sequencing of TP63 (NM_003722.4) identified a heterozygous c.730T>A, p.(Cys244Ser) variant, located in a mutational hot-spot in the DNA binding domain. R.H. Lekanne Deprez: None. Pot: None. We were able to figure out two clinical subgroups: while one part of the patients was continuously prone to serrated polyps, the other patients only showed a temporary polyposis with several inconspicuous colonoscopies afterwards. In the future, SMASH might be able to diagnose cancer e. The normalization of the data was performed by GeneSpringGX software. Giuliani: None. Conclusions: Most of the individual presented some symptoms of oligodontia-colorectal cancer syndrome. Bigeli Rafacho: None. Interestingly, males are significantly overrepresented, and thus we speculate that sex-linked traits could affect susceptibility to clinical penetrance and the clinical spectrum of SETD1B variants. Martínez-Hernández 4 1Metabolic Disease Laboratory, Genetic Department. Libraries were sequenced on a Sequel II System, and data was analyzed in NGSengine®.High quality data was generated for all samples. Gori: None. It is necessary to conduct more extensive studies the larger sampling. Validation of several proteins by immunoblotting is currently being performed. Methods: A total of 114 African Americans from SAGE and 144 Hispanics/Latinos from GALA II were included in the analyses. Barwinski: None. Method: We made clinical exome sequencing that contains4493 genes using Illumina NextSeq-500 sequencer with Sophia Genetics Clinical Exome Solution (CES) kit version-2. Hart: None. While the HOPS-specific subunit VPS41 has been reported to promote viability of dopaminergic neurons in Parkinson's disease, it has not yet been linked to human disease. Karlsson: None. Hazelwood: None. At 10 year old neurologic examination showed horizontal nystagmus and saccadic eye movements, face hyperkinesia, drooling, choreoathetosis, Romberg instability, gait ataxia. About 25-50% of intellectual disability (ID) is genetically determined, and X-linked ID (XLID) is a major pathogenic cause. In this study, we report novel pathogenic variants found in LSS. Long-term follow-up studies are needed to conclude for other cancer types, as well as a relationship with the extent of tissue mosaicism. Sanger sequencing and restriction fragment length polymorphism analysis was conducted to study recently found and novel variant segregation within the affected family. Hofmann: None. The frequency of the rs1800012 T allele was significantly higher in cases (40%) compared to that in the CON (6%, p A; Fisher's exact test, p = 0.0192) gene, which reached statistical significance in LCCLs group. Van Laer: None. Thompson24, Ella Wilkins8,25, Marjolein H. Omid: A. These were 8 missense mutations of KMT2D, SETD2, KDM6B and IDH1 and one silent variant of TET2. P07.023.C Identification of copy number variants relevant to primary immunodeficiency from exome sequencing data Rensheng Wan 1, Maximilian Schieck1, Winfried Hofmann1, Philipp H. Twins tested negative for mutations in main ALS-genes. We overlapped our splicing SNVs with variants from the HGMD database and found 90 exonic variants and more than 300 SNVs in introns. The resulting frameshift generated a tail of 36 additional amino acids at the protein C-terminus. Several inherited disorders have been associated with increased risk for development of moyamoya disease including the two RASopathies neurofibromatosis and Noonan syndrome. Grootenhuis1 1Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands, 2University Medical Center Utrecht, Utrecht, Netherlands. Interestingly, an important accumulation of rare variants in TFEB-regulated genes was observed in PD patients (85% vs 45%). We identified mutations in TP53 (47%), and the RAS family (46%) genes, of which KRAS and NRAS represented 39% and 7%, respectively, followed by APC (37%), and PIK3CA in 12% of samples. Khadzhieva 1,2,3, Dmitry S. Conclusions: African populations harbour population-specific genetic variants that may alter the expression of the RNA sensor, RIG-1. For the remaining 18 criteria, gene- or disease-based specifications and/or evidence strength modifications were made. Targeted NGS allowed molecular elucidation in 16 % of patients with proportionate short stature and minor skeletal features. Dedoussis: None. Heide: None. ChIP-Seq for MBD2/3 genome wide DNA binding pattern (e.g. promoters, gene control region, transcriptional enhancers, etc.) in untreated and HPV 16 E6/E7 shRNAs treated CaSki cell culture was performed and the results were analysed using Base Space Illumina apps. These manifestations are consistent with the ones presented in our patient. Ruzzenente: None. According to VarSome database, mutation c.412G>T (p.Ser138Ala), with the allele frequency 0.01% (ExAc) was predicted as benign. Renieri: None. Despite this striking clinicopathological concordance, the pathophysiological mechanisms remain largely unknown. P08.015.A Inherited variants in CHD3 demonstrate variable expressivity in Snijders Blok-Campeau syndrome Jet van der Spek 1,2, Joery den Hoed3,4, Lot Snijders Blok1,2,3, Alexander J. S.A. Vasilyev: None. Nykter: None. It is usually diagnosed in children with neuro-behavioral disorders; diagnosis in neonatal period has been described in only few patients.Clinical report. Vasilyeva1, E F. This is of paramount importance for the first- or second-degree relatives in which the identification of the pathogenic substrate, that renders them vulnerable to an increased risk for life-threatening cardiac events, including sudden death, might prompt for clinical and tailored treatments. Savage: None. The aim of this project is to establish a free and open access interactive, asynchronous training source in medical genetics: e-learners will be able to access an interface offering them different blocks of e-learning, self-assessment tools, and monitoring of learning achievement. Herms: None. Aborted sudden cardiac death (SCD) leading to HCM diagnosis occurred in one proband at the age of 68, and family history of SCD was reported by five (39%) probands. Case presentation: A now 22-year-old female patient, born of consanguineous parents, is presented. Lobanova: None. B.M. de Graaf: None. of Genetics, Riyadh, Saudi Arabia, 3KFSHRC, Dept. We conducted 59 Trio-WES, 1 Duo-WES, and 1 Single-WES analyses. However, the pace at which this research is occurring is significantly quicker than implementation. A substantial individual variation in the incidence of PM errors is likely to be related to the genetic background of the oocyte donor. Conclusion: According to our data, significant prevalence of VTE in association with thrombophilia was detected in postpartum period, compare to VTE during pregnancy. Three children with compound heterozygous variants at GJB2 and PAH were confirmed by Sanger sequencing. Solanes: None. Material and methods: Using the Fluorescent Activated Cell Sorting by which we isolated from head and neck cancer subpopulations endowed with stemness properties: CD44+/CD117+/133+ (CDs+), and ALDH+ enriched cells, besides their negative control group. Ramus: None. Pisarek: None. 0%). Patient 4 with a triplet of samples carried MLLT10-MKX, KMT2A-MLLT10 at diagnosis and relapse, no fusion in remission; also in relapse additionally emerged TBL1XR1-EAF2 chimeric trancript was detected. Pettersson: None. Rho GTPase-CDC42 plays a role in control cytoskeleton-dependent membrane rearrangements, transcriptional activation, secretory membrane trafficking, extracellular matrix and cytoskeleton remodeling. Dolzan: None. Karčiauskaitė: None. Final diagnosis: Methylmalonic acidemia vitamin B12-intact form. Among the eight foetuses with inherited ACH: 4 were diagnosed after early chorionic villus sampling, leading to termination of pregnancy (TOP) and 4 diagnosed after 26 weeks, by US.In the de novo prenatal 35 cases, mid-trimester US was normal in 80% of cases. Marasca: None. The suspension of physical and speech therapies has elicited a negative perception on parents about the evolution of these patients. To date, pathogenic variants identified throughout the gene explain more than 90% of the patients. Izzo: A. Espinós: None. Materials and Methods: A cohort of about 1000 individuals of European descent with described physical phenotype and collected lifestyle information will be examined using Infinium® Global Screening Array and Infinium® MethylationEPIC 850K microarray. Gogel: None. Gene-gene interactions were determined using the Multifactor Dimensionality Reduction method. Although ovarian cancers have been found to occur excessively in at least some families who have met criteria for LFS, their link to the syndrome is not definitely established. Remote access was not possible and the use of Unix terminal was intimidating for most biology students. There have been significant advances in gene therapies including Voretigene Neparvovec (VN), which was recently approved for intervention in RD due to variants in RPE65, by the Food and Drug Administration, and the National Health Service. P19.050.B Are highly pleiotropic variants of human traits enriched in genomic regions with strong background selection? Imbert-Bouteille: None. P02.044.A A burden of rare missense variants supports OTOG as a frequent gene in familial Meniere disease Pablo Román-Naranjo 1, Paula Robles-Bolivar1, María del Carmen Moleón2, Andrés Soto-Varela3, Ismael Arán4, Juan Manuel Espinosa-Sánchez2, Juan Carlos Amor-Dorado5, Angel Batuecas-Caletrio6, Paz Perez-Vazquez7, Alvaro Gallego-Martinez1, Jose Antonio Lopez-Escamez1,2,8 1Centre for Genomics and Oncological Research (GENYO), Granada, Spain, 2Department of Otolaryngology, Instituto de Investigación Biosanitaria, ibs.GRANADA, Hospital Universitario Virgen de las Nieves, Granada, Spain, 3Division of Otoneurology, Department of Otorhinolaryngology, Complexo Hospitalario Universitario, Santiago de Compostela, Spain, 4Department of Otolaryngology, Complexo Hospitalario de Pontevedra, Pontevedra, Spain, 5Department of Otolaryngology, Hospital Can Misses, Ibiza, Spain, 6Department of Otolaryngology, Hospital Universitario Salamanca, Instituto de Investigación Biomédica de Salamanca (IBSAL), Salamanca, Spain, 7Department of Otorhinolaryngology, Hospital Universitario de Cabueñes, Gijón, Spain, 8Department of Surgery, Division of Otolaryngology, Universidad de Granada, Granada, Spain. P17.021.D Deploying mouse resources for COVID-19 and related coronavirus research at Mouse Genome Informatics Anna V. The karyotype was normal (46,XX). Corà: None. Riedhammer1,2, Patrick Richthammer 1, Dominik S. Objective: Exosomes derived from mesenchymal stem cells (MSC) are critical players in the tumor niche being implicated in cell-to-cell communication affecting several hallmarks of cancer. N.E. Verbeek: None. Results: We identified 9 independent cQTLs (P A (p.Ala573Thr) in homozygous form. Jian: None. VariantAlert is easy to install locally or deploy remotely through the use of the Docker platform. Methods: We performed genetic testing of 460 patients with early-onset CKD of suspected monogenic cause using next-generation sequencing of a custom-designed kidney disease gene panel in addition to targeted screening for c.428dupC MUC1. Finally, we compared DMBT1 protein size from saliva, determined using Western blot, with DNA-based genotype of SRCR-domain number in a small cohort of healthy individuals to explore the relationship of the CNV encoding the SRCR-domain number to protein length. We aimed to establish the differences between germline and somatic variants. Recent technological feasibility of exome sequencing is enabling identification of rare variants of high penetrance, that refine previous findings and improve risk assessment and prognosis. Finally, we evaluated 16 non-coding impact prediction scores providing suggestions for variant prioritization. Our results strongly support once more the need for FISH and conventional karyotyping to resolve adequately these cases. Ranguin: None. P02.018.C LOXL1 and CACNA1A SNPs associated with exfoliation syndrome susceptibility in a sample of Northern Spanish population Leire Escudero-Arrarás 1, Araceli Lara-López1, María Rodriguez-Hidalgo1, Txomin Alberdi2, Iñaki Rodríguez-Agirretxe2,3,4, Javier Mendicute2, Javier Ruiz Ederra5,4 1Biodonostia Health Research Institute, San Sebastián, Spain, 2Department of Ophthalmology, Donostia University Hospital, San Sebastián, Spain, 3Instituto Clínico-Quirúrgico de Oftalmología, Bilbao, Spain, 4RETICS OFTARED, National Institute of Health Carlos III, Ministry of Economy and Competitiveness, Madrid, Spain, 5Miramoon Pharma-Biodonostia HRI, San Sebastián, Spain, San Sebastián, Spain. Martínez Hernandéz: None. Saraiva1,6 1Medical Genetics Unit, Hospital Pediátrico, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal, 2Medical Genetics Institute - UC Genomics, Faculty of Medicine, University of Coimbra, Coimbra, Portugal, 3CBR Genomics, Cantanhede, Portugal, 4Genoinseq, Next-Generation Sequencing Unit, Biocant, Cantanhede, Portugal, 5Center for Neuroscience and Cell Biology, University of Coimbra, Coimbra, Portugal, 6University Clinic of Pediatrics, Faculty of Medicine, Universidade de Coimbra, Coimbra, Portugal. DMBT1 shows extensive multi-allelic germline copy number variation (CNV) across all populations, with the tandemly-repeated CNV leading to different alleles with between (7-21) SRCR domains. Olivier-Faivre: None. Adolescents and young adults (AYAs) with LFS may experience barriers to addressing unique healthcare needs in the US healthcare system, requiring compensatory strategies to cope with emotional and financial strain. Cimbalistiene: None. A 229 Kb 3q29 microduplication, not overlapping the critical region for 3q29 duplication syndrome, was previously detected by CGH array in the patient and her healthy mother. Wilson, Nicola Pirastu University of Edinburgh, Edinburgh, United Kingdom. In addition, we compared the proportion of ART-conceived livebirths and parental ages at childbirth across patients with eight epi-IDs. We demonstrated that most ART-conceived patients with epi-IDs were found in Silver-Russell syndrome (SRS) and Beckwith-Wiedemann syndrome (BWS) patients, and parental ages were almost consistent in patients with eight epi-IDs. Conclusions: ART can be a risk factor for the development of epi-IDs for mothers aged ≥ 30 years. Therefore, we built a miRNA-based CMS-classifier by translating the existing mRNA-based CMS-classifier using machine learning. Until very recently, the p.Arg592Trp variant, either in the homozygous or compound heterozygous state, has been exclusively and repeatedly described in infants with severe cardiomyopathy or primary pulmonary hypoplasia, both resulting in death before the age of 1 year. Introduction: Life-threatening adverse drug reactions (ADRs) pose a significant health care burden. In this study, we compared the efficiency of indels formation in the EGFP gene and the c.337delG mutation correction efficiency in this gene via delivery of CRISPR-Cas9 in the plasmids and RNP. To investigate neuronal function at the cellular level we now performed electrophysiological experiments, inducing long-term potentiation (LTP) in hippocampal neurons from mutant and wild-type mice. Two widgets were also developed, ipycytoscape and ipyigv, to use Cytoscape and the genome browser IGV in Jupyter notebooks. Hoffer: None. Introduction: Despite comprehensive genetic testing, over half of the patients with genetic diseases remain molecularly undiagnosed. P17.028.C Resolving complex pathogenic alleles using HiFi long-range amplicon data and a new clustering algorithm John Harting, Cheryl Heiner, Ian McLaughlin, Lori Aro, Zev Kronenberg Pacific Biosciences, Menlo Park, CA, USA. Results: The variation p. Ciolfi: None. Russian prevalence of mild and severe HPP is still unknown. RT-qPCR validation additionally confirmed statistically significant higher expression of ELOVL7 in non-responders (p = 0.016; FC: 1.43). Cross4, Andrew H. Conclusion: The aCGH technique is a high-resolution laboratory setting that allows detection of pathological CNVs. Further studies are needed for complete understanding of the mechanism related to gene duplication in the onset and progression of the presented developmental and neurological disorders. Avci: None. Bignon: None. Perry2, ReproGen consortium (www.reprogen.org) 1Genetics of Complex Traits, University of Exeter Medical School, University of Exeter, Exeter, United Kingdom, 2MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Institute of Metabolic Science, Cambridge, United Kingdom. Kaplan: None. Saetta1 11st Department of Pathology, School of Medicine, National and Kapodistrian University of Athens, Ath, Athens, Greece, 2Department of Surgery Attikon Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece, 31st Department of Propaedeutic Surgery Hippokrateion Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece. Genetic Counseling is imperative to guide the couple in the best decision as well as to warn of the need for further analysis in the family. Mehnert: None. The low prevalence of variants in autosomal recessive genes suggests further research in African populations is necessary to identify non-de novo epilepsy-causing variants in those populations. For 19 known CAD loci, we showed that the probably causal genes are more distant from the top GWAS signal. If true, studies of CS may yield insights into the mechanistic basis of preeclampsia. Material and Methods: Two male newborns were referred to our genetic counselling for cryptophthalmos. M.B. Cicekdal: None. However, the involvement of such modifications in HSCR pathogenesis, is still largely unknown. Bonati: None. Abouelhoda: None. Our previous experience of teaching genomics was limited by available academic computational resources, restricting studies to unrealistically small datasets. Caudle: None. D'Asdia: None. Mingyan: None. Matomo: None. Gonçalves: None. She had development delay with fine rough motoric skills without significant hypotonia and signs of hyperactivity with poor vocabulary. Many genetic mechanisms are involved, of which the most frequent was the deletion of the maternally inherited 15q11.2-q13 region. We aim to investigate the impact of MHC MS-risk alleles on T-lymphocytes repertoire in MS. Matti: None. A.N. Kuzovlev: None. P14.029.B Increased methylation of genes responsible for fetal-maternal interaction in chorionic villi of miscarriages with trisomy 16 Stanislav A. E.G. Burchard*: None. Schönthaler: None. However, few studies with limited sample size or limited to specific pharmacogenes have explored the clinical utility of adding clinical pharmacogenetics interpretation to diagnostic WES. Kitajima1, Juliana Jordão1, Erika L. Gabonova: None. Csereoka: None. Kleiblová: None. The identified, novel pathogenetic or likely pathogenetic variant in POGZ include frameshift (5), stop (3), splicing (2) and missense (1) variants, mostly occurring de novo, except for a familiar case (3 subjects). Chung6, Alexa Geltzeiler6, Erin Torti7, Peter M. Amunts: None. Loderer: None. Contrò: None. Riva: None. An echocardiogram revealed a borderline thickness of the left ventricular wall (z-score: 2.4). Half of these mutations have been detected in exons 6 and 7 of the ECM1 gene. Introduction: Inverse-variance weighting (IVW) two-sample Mendelian Randomization (MR) is the most widely used method to estimate the causal effect of an exposure on an outcome. Martinez Soroa: None. Thus, they rather encode a truncated protein. Funding: MIUR INTEROMICS PB05. Li: None. Mahmood: None. Microarray showed pathogenic CNVs in 11 patients (17.7%): deletions at 1q, 16p11.2, 18q, 19p13.2, distal 22q11.21 and Xp11; duplications at 15q13 and 18q12 and a complex rearrangement in chromosome 13. Goksel Tulgar: None. Introduction: This review aims to give an overview of the prevalence and clinical presentation of lymphatic disorders in genetically proven Noonan syndrome. We conducted a qualitative study comprising a

series of focus groups with 21 neurologists and endocrinologists about their genetic testing practices in the western part of France. Considering to low prevalence, no clear correlation between mutations (genotype) and phenotype has been found. All the reported patients present truncating variants of HNRNPR, except one with the same heterozygous missense variant p.Arg588His as our patient. del Pozo: None. R.A. Siddiq: None. Lastivka: None. After variant filtering and prioritization, variants were confirmed by Sanger sequencing using primers unique to PKD1 or PKD2. Individual RO markers were integrated with LT and ERT as a risk. She showed neither neurological nor other symptoms of IP and suffered two miscarriages. Poulain: None. He presented facial dysmorphism and multiple congenital alterations. Markov: None. Niemira: None. of idiopathic ventricular arrhythmia (iVF), 34 arrhythmogenic cardiomyopathy (ACM; of which 27 right -/ 7 left predominant) and 2 have hypertrophic cardiomyopathy (HCM). P25.008.C HLA-A*11:01:01:01, HLA*C*12:02:02:01-HLA-B*52:01:02:02, age and sex are associated with severity of Japanese COVID-19 with respiratory failure Seik-Soon Khor 1, Yosuke Omae1, Nao Nishida2, Masaya Sugiyama2, Noriko Kinoshita3, Tetsuya Suzuki3, Michiyo Suzuki3, Satoshi Suzuki4, Shinyu Izumi5, Masayuki Hojo5, Norio Ohmagari3, Masashi Mizokami2, Katsushi Tokunaga1 1Genome Medical Science Project, National Center for Global Health and Medicine, Tokyo, Japan, 2Genome Medical Science Project, National Center for Global Health and Medicine, Chiba, Japan, 3Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo, Japan, 4Biobank, National Center for Global Health and Medicine, Tokyo, Japan, 5Department of Respiratory Medicine, National Center for Global Health and Medicine, Tokyo, Japan. Castillo-Villasana: None. Bolduc: None. Methods: We provide a mathematical rationale for a more clinically-meaningful formula for estimating penetrance. Labrecque: None. However, there is no consensus among its definitions. Obón: None. Functional annotation of miRNA and mRNA together corresponded to an aberrant expression of genes associated to the cell cycle and meiosis of male germ cells. Castilla-Vallmanya: None. Spinozzi: None. Conclusion: MID1 gene contributes with occurrence of cleft lip associated to ocular hypertelorism and this combination can be a mild form of the G/BBB syndrome. Makarov: None. It may also reduce the length of time infants and children require intensive care and prevent repeat inpatient admissions. Results: Analyses of genetic models revealed significant associations with GC risk: male patients with PLK2-rs9663615 CT genotype had lower risk, whereas female patients had higher risk (OR = 0.59, 95%CI = 0.37-0.93, P = 0.023; OR = 2.03, 95%CI = 1.09-3.80, P = 0.026, respectively). Another patient without prior NGS studies showed a SNV[X1] in ANKRD11 that was identified as responsible of the phenotype. Binder1,4 1Max Planck Institute of Psychiatry, Munich, Germany, 2Institute of Computational Biology, Helmholtz Zentrum München, Munich, Germany, 3International Max Planck Research School for Translational Psychiatry, Max Planck Institute of Psychiatry, Munich, Germany, 4Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA. VIP is open source, and we welcome community contributions to add novel tools and create new pipeline configurations suited to different use-cases. Andujar: None. J.L. Losso: None. We observed significantly weaker LTP in Ftsj1-deficient animals than in control littermates. Banu6, Mashaya Zaman6, Stephanie Efthymiou7, Henry Houlden7, Irma Järvelä8, Leena Lauronen9, Tuomo Määttä10, Isabelle Schrauwen11, Suzanne M. C.J. van Asperen: None. The actual haplogroup of the House of Osman is still controversial, the Ottoman dynasty might belong either the J2, or the R1a haplogroup. Mikhailova1,3, Kristina Ushakova1, Evgeny Tretiakov1,4, Andrey Yurchenko5, Vsevolod Makeev2, Dmitrii Knorre6,7, Sergey Nikolaev5, Ilia Mazunin8,9, Jacques Fellay10, Konstantin Khrapko11, Konstantin Gunbin1, Konstantin Popadin1,10 1Immanuel Kant Baltic Federal University, Kaliningrad, Russian Federation, 2Vavilov Institute of General Genetics RAS, Moscow, Russian Federation, 3University of Münster, Münster, Germany, 4Medical University of Vienna, Vienna, Austria, 5Université Paris Saclay, Villejuif, France, 6Moscow State University, Moscow, Russian Federation, 7Sechenov First Moscow State Medical University, Moscow, Russian Federation, 8Skolkovo Institute of Science and Technology, Moscow, Russian Federation, 9Moscow Institute of Physics and Technology, Dolgoprudnyi, Russian Federation, 10Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland, 11Northeastern University, Boston, MA, USA. Bocharova1, Ksenia V. Recent work using this system has identified a new subset of PIGG-dependent GPI-APs with an alternative bridging on the second mannose. This girl is the first in the family. Kuglik: None. Svetel: None. T2D loci and eQTL were mapped using positional cloning by LD; an association mapping method which utilises high-resolution genetic maps and multiple genetic variants to offer increased power over conventional single-SNP tests of association. Test samples of genomic DNA were extracted from PBMC of healthy volunteers. Additional studies with larger sample sizes are required to further elucidate the genetic contributions to translational symptom dimensions. Patterson3,4, Malcolm Wells5,4, Juan Gonzalez-Abraldes5,4, Matthew Smith5,4, Farshad Niri2, Lisa Prat2, Alison Eaton1,4 1Department of Medical Genetics, University of Alberta, Edmonton, AB, Canada, 2Genetics and Genomics, Alberta Precision Laboratories, Edmonton, AB, Canada, 3Department of Medicine, Division of Haematology, University of Alberta, Edmonton, AB, Canada, 4Stollery Children's Hospital, Alberta Health Services, Edmonton, AB, Canada, 5Department of Medicine, Division of Gastroenterology, University of Alberta, Edmonton, AB, Canada. Placentas were isolated on the gestation day 15 and day 20. All together, we concluded that the combination of both variants is the most likely cause of the disease in the child. Lin: None. Dubois d'Enghien: None. Conclusions: Association between polymorphisms of the genes and infection with different forms of tuberculosis were not identified in our research. Materials and Methods: 60 patients diagnosed with early-onset dementia (EOD) were tested by next generation sequencing targeted panel, which contained 127 genes associated to neurodegenerative disorders. Fortunato: None. D.D.M. Braat: None. Bove: None. Tommasi: None. Materials and methods: We have performed analysis for promoter methylation of 8 tumor suppressor genes (ATM, BRCA1, CDKN1a, MLH1, Msh2, Rara, Tp53, Xpc) in blood samples of patients with T2DM compared with controls with normal glucose tolerance. In 7 additional cases, we reported variants of unknown significance relevant to the patient's phenotype, which we strongly believe are responsible for the clinical features. Methods: Key clinical questions were identified and literature searches were performed using MEDLINE, Embase and Cochrane. The maternal grandmother has lumbar disc degeneration and hearing impairment. Forni: None. None. There is a different effect of mild versus severe mutations: Mild mutations increase the risk of developing PD by 2.2-fold while severe mutations increase this risk by 13.6-fold. Y.A. Barbitoff: None. Results: The main treatment was ET+CDK4/6 inhibitors (92%). E. Results: Specifications were developed for nineteen ACMG/AMP criteria while ten were not applicable. Results:A total of 29 survey responses were received. Buratti: None. Cecilia Poli27,32, Usha Kini24, Stephanie Efthymiou23, Jens Meiler35,36, Reza Maroofian23, Fowzan S. Ciliberti: None. Gerber: None. Here, we present a case with hypereosinophilia in whom an atypical FIP1L1-PDGFRA fusion pattern in bone marrow specimen was detected. All patients had at least a single HPO CNV-term match except one. Methods: Sixteen patients with different genetic syndromes were recruited. Kulvajtova: None. Han: None. P13.029.B Ring chromosome 22 in patients with 22q13 duplication, 22q13 interstitial deletion, and 22q13 terminal deletion Anthony Nemr 1, Tony Yammine1, Rita Esber1, Rita BouChedid1, Melissa Daou1, Georges Hilal1, Chantal Farra1,2 1Medical Genetics Unit, Faculty of Medicine, Saint-Joseph University, Beirut, Lebanon, 2Medical Genetics Department, Hotel-Dieu de France University Hospital, Beirut, Lebanon. Results: Tonkin: None. In addition, methylation status of SRS- and BWS- related DMRs may be vulnerable to the effects of ART. Here, we consider the extent to which eQTLs have also an immediate effect on translation and quantify the degree to which regulations of expression and protein levels share a genetic architecture. Progression free survival (PFS) was significantly longer in the low than in the high mtDNAcn ratio group: 1137 days vs 252 days (p T;p.(Gln128Ter) in TEX13B. Prota: None. Published: J.X.M. Cerqueira: None. The couple needed IVF. Kilpeläinen1 1Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Copenhagen, Denmark, 2Department of Public Health, Section of Epidemiology, Faculty of Health and Social Sciences, University of Copenhagen, Copenhagen, Denmark. We confirmed usefulness of ddPCR in the PIK3CA mutation assessment in FFPE samples. Gene carrying variants or alternative splicing events were also assessed differential expression. Smoking and BMI also had a significant influence on serrated polyp burden in our cohort. suggested Relapsing Encephalopathy with Cerebellar Ataxia (RECA) in children with ATP1A3 mutation. Introduction: According to the current data, bone-derived undercarboxylated protein osteocalcin (OCN) performs the function of a hormone regulating the systemic glucose metabolism. de Andrade: None. F.M.K. Williams: None. Johansson, Joeri K. Huntsman9, ERN-GENTURIS group, SOLVE-RD consortium, E. González-Zaldivar: None. Varicose veins (VVs) are a common venous pathology affecting over one third of adults worldwide. Conclusions: According to the ACMG criteria the variant c.2090G>A/p.Cys461Tyr in the GRIN2B gene is defined as pathogenic. Roorcyk: None. The binding of candidate miRNAs on polymorphic allele was evaluated with Luciferase reporter assay. De Wit: None. Conclusions: We found that isolated polysyndactyly is a common phenotype of inherited as well as de novo GLI3 mutations and is not restricted to mutations in the last third of the GLI3 gene. Conclusions: A pre-CMA test interactive web-based educational tool is well received and used to support women/couples and assists in making informed decisions regarding the disclosure of complex genomic-results. Among the genetic tests no alterations was identified by array-CGH and NGS-panel for cortical malformations, but whole-exome sequencing revealed the presence of a previously unreported de novo pathogenic variant in the CEP85L gene (c.232+1delG, NM_206921). Pathogenic bi-allelic variations of GTOF result in autosomal recessive deafness DFNB9. Balding: None. Prabhakar: None. Development of chromatin conformation study techniques identified several long-range regulatory elements of CFTR gene. Badman: None. Methods: Aiming to generate data on national and global levels, questionnaires on opinions were filled out (1) before and after dialogue (T0 & T1; n = 33) by a subgroup of visitors, (2) before or after dialogue by subgroups of people who had either signed up for dialogue (T0; n = 283) or who completed the questionnaire after they entered in dialogue (T1; n = 110), and (3) in August 2019 (T0; n = 1172) and April 2020 (T1; n = 1209) by independent samples from the Dutch population. By age 75, we estimate SORL1 LoF variants to reach a 100% penetrance only among homozygous APOE4 carriers (75% among APOE4 heterozygous carriers and 30% among APOE33 genotype carriers). Rombout: None. Johannesen: None. Both parents were carriers of the variant in heterozygous form. Materials and Methods: A genome-wide association study (GWAS) was performed in ~23,000 participants with NMP from the UK Biobank and a subtype analysis including only NMP with inflammatory symptoms. Most cases are sporadic. Conclusions: It remains unclear which variants in LSS lead to an alopecia phenotype only, and which lead to accompanying severe neurodevelopmental and dermatological phenotypes. We performed exome sequencing in a patient presenting with cutaneous and bone syndactyly and negative array-CGH and limb malformations panel results. Pilling1, Christine J. Provel: None. Our study was aim to investigate the prevalence, distribution, and antimicrobial susceptibility rates of MDR bacteria in patients with NI from some hospitals in Jeddah city. Moreover, we discussed the implication of flanking genes and X inactivation on the differential features or expressivity of the phenotype. Poncet: None. Physical examination showed plagiocephaly, bilateral temporal depression, hypertelorism, downslanting palpebral fissures, low-set ears, depressed nasal root, bulbous nasal tip, anteverted nostrils, retrognathy with chin dimple, short neck, sacral dimple with hypertrichosis. Further research is needed to develop personalized methods of perinatal loss prevention. Next generation sequencing has facilitated predictive genetic testing of at-risk relatives. Employment (full or part-time); Significant; Fleury Medicina e Saude. Campion: None. Even though UPDs do not necessarily have a pathogenic effect an increased disease risk due to imprinting effects is reported. Hiel: None. Slavíková: None. We have identified a relevant biological miR-146a-TRAF6 axis association in LN renal fibrosis progression. Results: Transcriptome analysis showed a similar LAMA2 gene expression in the atypical patient, the affected sibling and patients with absent merosin. Jhangiani: None. A total of 78 genes were selected for inclusion in the gene panel. Yogev: None. In a next step, the data of genetically unsolved cases will be harmonized and reevaluated. We further estimated the causal effect of estradiol on bone mineral density (BMD) using Mendelian randomization. Four different germline MET pathogenic variants were highlighted and three of them were already reported (MET p.(His1112Arg); MET p.(Val1238Ile); MET p.(Tyr1248Cys)). Introduction: Current cellular genetic models for Non-Alcoholic Fatty Liver Disease (NAFLD) have limitations that prevent the scalable investigation of gene variants. Karyotype confirmed the diagnosis and showed 47,XX,t(6;21)(q13;q22),+21 which was inherited from a balanced maternal translocation.Prenatal diagnosis was indicated in the next pregnancy and the fetal karyotype was normal (46,XX). Kilpeläinen: None. Boland-Auge: None. Conclusions: Bi-allelic variants in VPS41 result in lysosomal dysregulation that impacts multiple brain cell types, affects cerebellar function, and contributes to neurodevelopmental disease in humans. P11.054.D The Wales Infants' and childreN's Genome Service' (WINGS): Diagnostic rapid whole genome sequencing for unwell children with a suspected rare genetic diagnosisEmily Sloper, Oliver Murch, Jana Jezkova, Megan Fealey, Joseph Halstead, Thomas Stoneman, Elle McNeil, Angharad Williams, Michelle Wood, Katherine Burke, Siva Oruganti, Jennifer Calvert, Hywel Williams, Caroline Pottinger, Francis H. All variants were detected in the pre-treated pool at a similar abundance, confirming their optimal integration and representation. Rassoulzadegan: None. Ekici1, Pauline Hoá3, Frank Behrens7, Michaela Köhm7, Georg Schett8, Jürgen Rech8, Gunter Assmann9, Ali Nimeh10, Leonid Padyukov11, Gerd-Marie Alenius12, Neil J. Álvarez Garcia: None. P25.014.A Design of a cost-effective diagnosis tool for SARS-CoV-2 variant detection through a next generation sequencing (NGS) based strategy Mª Mercedes Montero 1, Paur Rodríguez1, Juan Ramón González2, Lluís Armengol1, Jairo Rodríguez1 1Quantitative Genomics Medicine Laboratories (qGenomics), Esplugues de Llobregat, Spain, 2Barcelona Institute for Global Health (ISGlobal), Barcelona, Spain. MR analysis confirmed several previously hypothesised risk factors such as socioeconomic status, however we found little evidence for many of the others. Mintoff: None. This observation supports the increasing interest in the identification of splicing variants, particularly those predicted as synonymous, which are often systematically categorised as benign. Barr: None. A diagnosis could then be made as the variant was previously reported as probably pathogenic for spastic paraplegia type 4. Therefore, it is necessary to discuss the addition into laboratory report of PVs in genes not from the recommended list. Materials and Methods: 18 months old girl was referred our clinic because of increasing creatinine kinase that found incidentally. Almagueer-Gotay: None. Clinic University Hospital of Valencia, Spain. Yosry: None. Joint hypermobility, cervical spinal fusion, EEG abnormalities and epilepsy also occur. Bigot: None. Mir: None. Results: We identified mutations in genes associated with CLL, such as SF3B1, ATM, RPS15, MED12, NOTCH1, or NFKBIE, but also a large number of non-recurrent mutations, which expanded or diminished differently after specific types of therapy and in relation to TP53 mutation profiles. N.G. Gorovenko: None. Materials and methods: In our ongoing pilot study, DNA was prepared from blood samples collected from 79 patients of European origin with diagnoses of acute and chronic pancreatitis, or pancreatic cancer. Results: Out of 421 women 43(10.22%) had VTE, 17(4.04%) during pregnancy and 26(6.18%) postpartum. He was referred to genetic evaluation because of the mental retardation, hypotonia and epilepsy. P12.185.A Cancer spectrum and penetrance in a cohort of patients with a loss-of-function germline SMARCA4 alteration Nienke van Engelen 1, Jozef Zsiros1, Saskia M. We target GJB2 cis-acting elements with dCas9-KRAB. This pandemic has had substantial influences on all aspects of life. P12.149.A NTHL1-tumor syndrome in Slovenian patients with adenomatous polyposis Iva Opalic 1, Ksenija Strojnik2, Mateja Krajc2, Marta Banjac2, Vida Stegel3, Petra Skerl3, Vita Setrajcic Dragos3, Gasper Klancar3, Srdjan Novakovic3, Ana Blatnik2 1University Medical Centre Maribor, Maribor, Slovenia, 2Cancer Genetics Clinic, Institute of Oncology Ljubljana, Ljubljana, Slovenia, 3Department of Molecular Diagnostics, Institute of Oncology Ljubljana, Ljubljana, Slovenia. Sánchez Soler: None. Idani: None. Glasova: None. This suggests presence of potentially clinically meaningful CNVs in 11.5% of this PAD cohort. Nuel: None. Correia: None. Introduction: Arthrogryposis multiplex congenita (AMC) defines phenotype when contractures are present in ≥ 2 joints. Rare variants with a CADD score>15 (coding) or a funseq2 score>1.5 (regulatory) were selected for further analysis with a Bayesian-based rare variant association test (BATI) using the discrete mRs scores (0-6, where 6 indicates death) as outcome. Background: Classic ataxia-telangiectasia (A-T) is characterized by progressive cerebellar ataxia beginning between ages one and four years, oculomotor apraxia, choreoathetosis, telangiectasias of the conjunctivae, immunodeficiency, and frequent infections. Halpern: None. Materials and methods: Ovid Medline, Embase, and Cochrane CENTRAL were searched for studies reporting on universal MMR IHC, followed by MMR germline analysis, until March 20, 2020. Introduction: Chronic Intestinal Pseudo-obstruction (CIPO) is a congenital enteric disorder characterized by severe intestinal dysmotility without mechanical obstruction. The lack of effective disease-modifying drugs and preventive tools highlights our incomplete understanding of the fundamental biological aspects of this disorder. Molecular pathway analyses were performed within STRING to investigate patterns of gene function in syndromic OC and across OC types. Karanlik: None. P13.004.A Looking back on copy gains: a retrospective review of clinical relevance and classification strategies Sónia Custódio, Rosário Silveira-Santos, Raquel Rodrigues, Eva Rolo, Juliette Dupont, Patrícia Dias, Oana Moldovan, Catarina Machado, Márcia Rodrigues, Mariana Soeiro Sá, Ana Berta Sousa, Ana Sousa Serviço de Genética Médica, Departamento de Pediatria, Hospital de Santa Maria - Centro Hospitalar Universitário Lisboa Norte, Lisboa, Portugal. Pi Castán: None. Bushe: None. Hence, CYHR1 is likely to be a novel key factor in human brain development due to impaired autophagy and spliceosome function. In order to validate the RNA extracted with Opentrons can be sequenced, the viral RNA sequence was aligned to a known SARS-CoV-2 sequence. Lakeman 1, Mar Rodriguez-Girondo1, Andrew Lee2, Antoinette Hollestelle3, Marjanka K. Conclusion: Greater oleate-induced increases of intracellular lipids in iPSCs with the NAFLD risk alleles indicate that undifferentiated iPSCs are a reasonable, more efficient substitute for hepatocytes when studying cellular lipid accumulation and an informative cellular model for the functional characterization of NAFLD genetic risk variants. Morandi: None. Genetically predicted BMI was linked to more sedentary time (P = 6x10-4), indicating bidirectional causality. J.E. Posey: None. Rare diseases comprise a diverse group of conditions, most of which involve genetic causes. Zhernakova: None. Whole exome sequencing was performed on two DNA pools, one constructed with DNA from AD patients and the other with DNA from healthy age-synchronized individuals. T.P. McVeigh: None. T.A. Vasilyeva: None. Knoers1, Genomics England Research Consortium, Patrick Deelen1, Lude Franke1, Albertien M. Roessler: None. Wojciechowska: None. Methods: Histopathology/morphology tumour information was obtained from ovarian cancers, in BRCA1/2 pathogenic variant carriers (n = 1,942) and BRCA1/2 non-carriers (n = 2,616). Cieślikowska: None. Roman: A. Methods: PPi levels of 128 blood samples (92 [62 patients], 22 [21 carriers] and 14 [14 controls]) were measured. 6 cases had to be excluded from further analysis due to limited data. V.M. Siu: None. Fluent BioSciences has developed Pre-templated Instant Partitions (PIPs) to simultaneously segregate complex cell mixtures into partitions with barcoded template particles that can be easily processed for scRNA-Seq (PIPseq) without the need for complex instrumentation or microfluidic consumables. Of the 93 cases with isolated CFMs, four (4.3%) clinically significant pathogenic CMA results were detected, a rate slightly increased compared to the control population (RR 3.17 (95% CI 1.02-9.83)). We therefore describe a national cohort of individuals carrying germline SMARCA4 alterations and their cancer phenotype. Although the TOP3B gene is not defined as the genotype of a particular disease in OMIM, its pathogenic variants have been associated with epilepsy, cognitive and behavioral disorders. Petrikis: None. Additionally, we refined CHD subtypes using genotype-phenotype correlations and six subtypes were proposed to be more genetically homogeneous. P.B.T. Neerincx: None. Ownership Interest (stock, stock options, patent or other intellectual property); Significant; Invitae Corp.. Y.J. Vos: None. Promising lncRNA could be considered as new therapeutic tool to control specific T cell immunity. Park: None. Results: X-rays showed dolicocephaly, ossified metopic suture, widening of the bregmatic fontanella and of the sagittal and lambdoideal sutures, perisutural calcified spots. Cheema: None. H.G. Ijntema: None. The follow-up was possible for only 59% of patients. We use a set of 26 genomic features combining epigenetic profiles, species conservation and density of disease and non-pathogenic variants to train the hyper-ensemble random forest model hyperSMURF (Petrini A. C. A. Bacino: None. P12.140.D MUTYH-associated polyposis in a cohort of Slovenian patients with adenomatous polyposis Ksenija Strojnik 1, Iva Opalic2, Mateja Krajc1, Marta Banjac1, Vida Stegel3, Petra Skerl3, Vita Setrajcic Dragos3, Gasper Klancar3, Srdjan Novakovic3, Ana Blatnik1 1Cancer Genetic Clinic, Institute of Oncology, Ljubljana, Slovenia, 2University Medical Centre Maribor, Maribor, Slovenia, 3Department of Molecular Diagnostics, Institute of Oncology, Ljubljana, Slovenia. However, in approximately 70% of the cases no causative variant(s) can be identified. P04.053.B Targeted next generation sequencing substantially advances molecular diagnosis of Marfan and Marfan related disorders Darina L. Martinez-Perez: None. Allelic, genotypic and haplotype association analyses with disease risk and reproductive risk factor were performed under the additive model. Small: None. Results: In 4/72 (5.6%) polyposis patients, all female, biallelic PV in MUTYH gene were identified; clinical characteristics are detailed in the table below. Three themes were identified: 1) technical and logistical issues, 2) communication issues 3) clinical content and outcome of the session. Funding: ISCIII (PIE14/00061), CIBERER. Study with a larger number of patients, or meta-analysis of previously reported studies, could give more precise insight in correlation of phenotypic features and pathogenic CMA results in this specific group of patients. W.P. de Boode: None. Lausch: None. fudulu: None. Introduction: Single cell RNA sequencing (scRNA-Seq) has made profound impacts in the study of cellular and molecular diversity in complex tissues. Grants: Horizon 2020 (No846502), Novo Nordisk Foundation (NNF18CC0034900, NNF17OC0026848), Danish Diabetes Academy (NNF17SA0031406). Kleefstra15, L. Martinez: None. The 58.33% of the cases remain undiagnosed and further studies are needed to identify the genetic cause of the hearing impairment in these patients. P05.023.A Hereditary Haemorrhagic Telangiectasia: evidence of a common ancestor in 19 families from Northern Italy Anna Sbalchiero 1, Yasmin Abu Hweij1, Tommaso Mazza2, Elisabetta Buscarini3, Fabio Pagella4,5, Elina Matti4, Guido Manfredi3, Giuseppe Spinozzi4, Sara Ugolini4, Carla Olivieri1 1General Biology and Medical Genetics Unit, Department of Molecular Medicine, University of Pavia, Pavia, Italy, 2Unit of Bioinformatics, Fondazione IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italy, 3UOC Gastroenterologia- Centro di riferimento HHT, ASST Ospedale Maggiore di Crema, Crema (CR), Italy, 4Department of Otorhinolaryngology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, 5Department of Otorhinolaryngology, University of Pavia, Pavia, Italy. Gronskov: None. We searched for rare variants in 1665 genes: PP-causative (53), Hg-linked genes for lipoprotein function (128), TFEB-regulated (428) and Mitocarta 2.0 (1158). Results: Our analysis detected 37 DE miRNAs and 738 DE mRNA. Marcos-Asensio: None. Piazza: None. Iftimovici: None. Introduction: The utility of next-generation sequencing (NGS) technologies in the field of rare diseases has already been proven, improving the molecular diagnosis rate. In particular, a paracentric inversion at 2q24.3 was shown to disrupt SCN1A gene, associated to Dravet syndrome. F.N. Tilemis: None. Bataneant 1, Adela Chirita-Emandi2, Estera Boeriu2, Mihaela Baica2, Andreea Beloiа2, Patricia Urtila2 1University of Medicine and Pharmacy "Victor Babes", Romania, Romania, 2University of Medicine and Pharmacy "Victor Babes", Timisoara, Romania. Hardiman: None. The genetic mechanisms were 15q11-q13 microdeletion (30/44), UBE3A mutations (8/44) and maternal UPD15 (3/44). SGO received funding by CONADI and TYM by Minciencias. Reimer: None. Here we report a preterm male with postnatal severe respiratory problems, hepatosplenomegaly, bilateral hydroceles, anemia, hyperbilirubinemia, but no neurological abnormalities. She was the first child of healthy non-consanguineous parents. A 9-month-old male patient was admitted to our clinic with short stature, mild hair, developmental delay and recurrent infections. Three DBD-variants had decreased DNA binding ability (A p.(Glu127Lys)). Bradshaw2,3 1Center for Human Genomics and Precision Medicine, University of Wisconsin, Madison, WI, USA, 2Genetics and Genome Biology, The Hospital for Sick Children, Toronto, ON, Canada, 3Department of Molecular Genetics, University of Toronto, Toronto, ON, Canada. Several patients' organizations were formed and more are underway. Bispo: A. P.I. Golikova: None. Lipsker: None. Liley: None. Interactions between ncRNAs and methylation were demonstrated. This approach is useful to detect tumor somatic mutations in gynecological minimally-invasive samples at high sensitivity. T.F. Hansen: None. Methodology: The aCGH was performed using Affymetrix Cytoscan 750K. Patzer: None. A. S. Koltsova: None. Here, we benchmark novel ultra-fast WGS data analysis pipelines. Based on the identification of new candidate genes, the increase of phenotypic spectrum of the diseases diagnosed (even reporting cases with a dual diagnosis) and the finding of novel pathogenic variants, in 5% of cases, we recommend going beyond the basic pipeline previously used for routine analysis, especially in cases with a strong suspicion of an underlying genetic disease and a previous inconclusive WES result. For germline testing, DNA was extracted from blood and NGS sequencing was performed using Nextera DNA Library Preparation Kit in combination with Illumina's TruSight_Hereditary_Panel. Genotyping of the FTO and LPL genes were performed using PCR-amplified fragments. In the remaining 33 patients, we performed comparative computational analysis of confocal microscopy images and experiments related to protein function. Monteil20, Charlotte W. The proband's brother had multiple fractures and joint blockage since childhood, and 1 maternal uncle had joint blockage since childhood. Background: Inherited cardiac conditions (ICC), comprising primarily cardiomyopathies and cardiac ion channelopathies, predispose to sudden cardiac death. We analyzed 517 individuals from 10 populations of Northern Eurasia (Bashkirs from the Arkhangelsk region of the Republic of Bashkortostan, Bashkirs from the Burzyansky region of the Republic of Bashkortostan, Tatars, Chuvash, Balkars, Karachays, Kalmyks, Mordvins, Evens and Kazakhs). It has also lead to the identification of a heterozygous HECW2 variant in a patient with intellectual disability and severe autistic features. Ozunu: None. Physicians need help to deal with the rapid development of genomic medicine as most of them have received no specific training on the medical, ethical, legal and social issues involved. Highlights from the aggregation of cancer genomic profiling data and the associated annotations will be presented. Alkhzouz: None. DNA was isolated from amniotic fluid. For women we recommended mammograms (100%), MRIs (100%), breast ultrasound (85%), serum CA-125 (61,7%), transvaginal ultrasound (59,6%), chemoprevention (61,7%), bilateral risk-reducing mastectomy (100%) and risk-reducing salpingo-oophorectomy (100%). Legius: None. Mang: None. His parent's chromosome analysis is normal. Purpose: Gain a knowledge of the link between VVs of lower extremities and knee OA, but it is unclear if there are causal relationships between the disorders. M.J. Diniz: None. Results: Minor allele frequencies for SNPs rs3817621 (C), rs79334031 (A) and rs2072597 (C) were 0.213, 0.038 and 0.263, respectively. Sharkova: None. Furthermore, F-actin recovery after latrunculin B treatment was impaired, indicating that MAPKAPK5 is implicated in F-actin polymerization. Materials and Methods: A whole-genome oligonucleotide microarray (Agilent Technologies 60K and 180K) was applied to a cohort of 239 unrelated patients phenotypically characterised with various type of (with or without other neurodevelopmental disorders such as developmental delay, intellectual disability, autism or other neurodevelopmental disorders). Kivelä2, Marjukka Myllärinen3, Juha A. Whole-exome sequencing has proved an adequate tool to assess these heterogeneous disorders. Van Walderveen syndrome 2 is an autosomal recessive disease characterized by intellectual disability, dysmorphic craniofacial features, auditory malformations resulting in hearing loss, and limb malformations. Several, often unexpected traits, significantly correlated with all components of the syndrome (n = 314). Two patients harboured the other 2 variants, (c.9001_9002delAG resulting in p.Ser3001Phefs*6) and (c.9066delA resulting in p.Glu3023Alafs*10). To date, there is evidence that impaired membrane transport can play an important role in the pathogenesis of PD; therefore, in our work we have analyzed changes in the relative mRNA levels of the DNM2, EPN2 and EXOC4 genes in the peripheral blood from treated and untreated patients with PD. Garros-Regulez: None. Seven individuals are known affected family members. Here, we perform a CRISPR-based screening along the topological associated domain (TAD) of SCN5A in order to identify novel regions involved in the control of its expression and activity and topology. All the pipelines of solida-core are built, as a first step, following the GATK Best Practices for DNA and RNA sequencing analysis. Up to 70% of LFA is encoded in a hypervariable copy number variation (CNV) named "Kringle IV type 2" (KIV-2) CNV. Dorosz6e: None. QIAGEN's GeneGlobe Data Analysis Centre was used to perform the data analysis. Speech delay was noticed at two years old and then fluent speech was significantly delayed. There are over 55,000 variable number tandem repeats (VNTRs) in the human genome. P23.015.C Implementing the use of genetic information in the electronic health record: a scoping review on the ethical and legal framework in the European contextPaola Del Sette, Marco Salivetto, Camilla Tettamanti, Rosagemma Ciliberti, Emilio Di Maria University of Genoa, Genova, Italy. P06.053.B Expanding the clinical spectrum of primary coenzyme Q10 deficiency type 7: the first case with cardiomyopathy Lisette Leeuwen, Charlotte M. Z.F. Nagy: None. Within pharmacogenetic polymorphisms, which are highly dependent on ethnicity, play a major role in the function of CYPs and lead to various pharmacogenetic phenotypes divided into poor, intermediate, extensive, and ultrarapid metabolizers. Supported by MH CZ - DRO, Motol University Hospital, Prague, Czech Republic 00064203 N. The normal initial therapy of patients with LPI is protein-restricted diet and supplemental L-citrulline) does not change the signs of low bone mineral density. Funded by the Wellcome Trust, Department of Health and by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC). Epigenetic modifications, such as DNA methylation, are known to play crucial roles in the development of the enteric nervous system (ENS). Fernandez-Jimenez: None. D'Alessandro". University of Palermo, Palermo, Italy, 11Department of Genetics, Reference center for Rare Diseases and Developmental Anomalies, Caen, France, 12Seaver Autism Center for Research and Treatment, Icahn School of Medicine at Mount Sinai, New York City, NY, USA, 13Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York City, NY, USA, 14The Mindich Child Health and Development Institute, Icahn School of Medicine at Mount Sinai, New York City, NY, USA, 15Department of Medical Genetics, Sant'Orsola Hospital, University of Bologna, Bologna, Italy, 16Department of Pediatrics and Public Health and Pediatric Sciences, Turin, Italy, 17Clinical and Biological Sciences Department, University of Turin, Turin, Italy, 18Radiation Oncology Branch, National Cancer Institute, Bethesda, MD, USA, 19Unit of Medical Genetics, "Città della Salute e della Scienza" University Hospital, Turin, Italy. Sánchez-Guiu: None. Löwenheim: None. Hagelstrom: None. Loterszstein: None. We calculated PRSs at three thresholds for SNP inclusion (pT): pT = 0.5 (Escott-Price et al. P09.120.A Oxytocin receptor gene and CD38 gene polymorphisms association with social functioning in schizophrenia Vera Mikhailova 1, Tatiana Lezheiko 1The Mental Health Research Center (MHRC), Moscow, Russian Federation, 2Research Centre for Medical Genetics, Moscow, Russian Federation. 9 children were born from the second and later pregnancies. Hauteclocque: None. Results: The focus group resulted in family criteria focusing on cardiovascular events (i.e. sudden death, any cardiac disease, implantable cardioverter-defibrillator) at young age in one or more close relatives. Byrne 1, Wouter van Rheenen2, Jan H. Introduction: Individuals with Lynch syndrome have a pathogenic germline variant affecting one of the mismatch repair (MMR) genes (MLH1, MSH2, MSH6 or PMS2) and are often recognized by MMR-deficient (dMMR) colorectal or endometrial cancers. Herein, we investigated associations between genetic variants and a PRS for prostate cancer (PRCA), a highly heritable and polygenic disease. The most frequent variants were X-linked KAL1 caused by 32 different COL4A5 variants (75%). We also show that European ancestry participants are more overrepresented in PGS studies than what has been previously observed for GWAS, and outline future systematic curation efforts. Transiently expressed wild-type CYHR1 was exclusively observed in the nucleus, however, mutant protein was reduced and found in cytoplasm. Our findings demonstrate the relevance of constitutive activation of TFEB and TFE3 in the growth of kidney tumors associated with BHD syndrome and encourage future studies exploiting TFEB/TFE3 inhibitors as a therapy for these tumors. Vilhjálmsson: None. BRAF, MEK1 and MEK2 are the most frequently genes involved. In this study, we selected and performed in vitro characterization of variants in non-coding region 3'UTR of LDLR, a non-canonical region not screened in routine and that could contribute to genetic diagnostic. We hypothesize that this mechanism contributes to the 'epithelialisation' of the corneal endothelium observed in PPCD1 and may therefore represent a target for future therapeutic interventions. P01.033.A The FTO gene and adolescent puberty Elena Mashkina, Maria Amelina, Michail Shkurat Southern Federal University, Rostov-on-Don, Russian Federation. Results: We present a 4-year old girl with following dysmorphic signs - downward corners of the mouth and large oral opening, saddle nose with wide nasal root, retracted eye bulbs, triangle pointed eyebrows, asymmetrical placement of the eyelid, smaller opening of the lid, asthenic pointed forehead, short philtrum, chin and sparse hair. Nogué: None. Our results of Ne in the Lithuanian population through time demonstrated a substantial reduction of Ne over the 150,000 - 25,000 years before the present (YBP). Instituto Murciano de Investigación Biosanitaria (IMIB-Arrixaca), El Palmar (MURCIA), Spain, 2Instituto de Investigación Biomédica en Red de Enfermedades Raras, ISCIII, Madrid, Spain, 3Centro de Genética Médica. With the support of ERN ITHACA and UNESS (Digital University for Health and Sport), the content of the MOOC is currently being revised and translated into English to be launched in mid-2021 in a bilingual French-English version. We performed genome-wide linear regression in SiGN (without inclusion restrictions on age) to analyse AAO of IS limited to cases of European ancestry. Tel Hashomer camptodactyly syndrome is a genetic syndrome characterized by camptodactyly, skeletal dysplasia, and abnormal palmar creases. Haplotype analyses in 15 families suggested that c.694T>G/p.(Phe232Val) was a founder variant. Consequently, GWAS discovery is currently hampered by the lack of statistical power to detect weaker associations. Salakhov1, Magomed O. Speakers Bureau/Honoraria (speakers bureau, symposia, and expert witness); Modest; Modernat. P17.074.A KidneyNetwork: Using kidney-derived gene expression data to predict and prioritize novel genes involved in kidney disease Floranne Boulogne 1, Laura R. Almalki: None. Civera-Tregón: None. Funding: Instituto de Salud Carlos III (ISCIII)/FEDER funds: PI15/01824, PI16/00998, PI18/00362, PI19/01633, RETIC RD16/0006/0019, and Plataforma ISCIII Biobancos PT20/00196. Bähr: None. We classified carriers based on HDGC clinical criteria and variants according to CDH1/ACMG/AMP guidelines and performed genotype-phenotype analysis. In pathological studies, the extent and type of atherosclerosis are commonly assessed based on histological plaque characteristics that are linked to plaque rupture and erosion. Little is known about the phenotype in double heterozygotes who carry PVs in both genes. Method: We review the outcomes from the first 3 years of a newly formed paediatric rheumatology and genetic multi-disciplinary clinic. Introduction: The making of decisions by parents about genetic testing or about continuing a pregnancy in the face of genetic risk is often difficult. O.V. Bocharova: None. In view of these findings, a familial form of HS with variable expressivity was suspected and molecular genetic studies were carried out. We present a family in which both parents have relatively mild gastrointestinal symptoms, and two sons have severe PIPO, consistent with autosomal recessive inheritance. Our data confirm that the CRISPRi screening system is suitable for the precise characterization of SCN5A regulatory regions. Material and methods: The combination of DNA- and RNA-sequencing led to the identification of the defective MLIP gene. P12.153.A Use of machine learning and protein topology Characteristics to aid classification of Variants of Uncertain Significance (VUS) in the BRCA1 and BRCA2 genes Denise O' Mahony 1,2,3, Susan J. P09.010.C Identifying serum biomarkers of neurological disorders using whole genome sequencing Grace Png 1,2, Andrei Barysenka1, Linda Repetto3, Pau Navarro4, Xia Shen5,6,7, Emmanouil Tsafantakis8, Maria Karaletheri9, George Dedoussis10, Anders Mälarstig11,12, James F. Conclusions: These results may be used to inform BRCA1 and BRCA2 variant classification, with potential implications for patient management. P04.044.D Incontinentia pigmenti and favism due to a large genomic deletion including IKBKG and G6PD Maria Grossmann 1, Stephanie Spranger2, Snjezana Rendulic3, Andrea Bier1, Silke Reif1, Manuela Timmer1, Christian Jänecke1, Vivien Klaschka1, Jens Plaschke1, Stefan Krüger1 1Gemeinschaftspraxis für Humangenetik, Dresden, Germany, 2Praxis für Humangenetik, Bremen, Germany, 3Praxis für Humangenetik und Prävention, Stuttgart, Germany. Methods and Results: Through international data sharing, we identified 13 individuals presenting with neurodevelopmental disorders (NDDs) and carrying heterozygous likely damaging variants in ARFGEF1, identified as a candidate research gene after negative clinical exome analyses. P11.042.D Small deletion in the CREBBP gene detected in a fetus with short long bones, abducted thumbs and nuchal edema Silvia Serafim 1, Barbara Marques1, Sonia Pedro1, Ana R. Laver 1, Matthew N. To further investigate the NGS approach to characterize circulating miRNAs in plasma acquired from Bilateral petrosal sinus sampling (BIPSS) - a gold standard in diagnosis of ACTH secreting PitNETs. Materials and Methods: We sequenced plasma miRNA samples acquired prior and during BIPSS from both cavernous sinuses from inferior and complementary plasma from peripheral blood (before CRH administration, 5 and 15 minutes after stimulation). Intra-class correlation coefficient (ICC) was used to estimate the inter-rater reliability between English-Chinese translations, and between CSRI-Ra and electronic patient record (ePR). The NCSTN deletion was not identified in a local reference dataset comprising 60 ethnically matched whole exome sequences. We regressed nine CVD risk factors and subtypes on their respective polygenic scores (PGS) and exposure to childhood maltreatment using linear and logistic multivariate regression, adjusted for sex, age and 40 genetic principal components. Introduction: Autoinflammatory syndrome (AIS) constitutes a heterogenous group of disorders defined by recurrent episodes of systemic inflammation in the absence of pathogens, autoantibodies and/or self-reactive lymphocytes. Eight loci contained genes coding enzymes with a known role in N-glycan biosynthesis, while 23 loci, including 16 novels, may contain regulators of protein glycosylation, including transcription factors, transporters, blood group antigens, and PDLs for glycosylated proteins. Conventional-karyotype and microarray analyses were normal. Conclusions: We provide evidence that genetic susceptibility to some diseases was related to genetic predisposition to COVID-19 complications specifically in women. Acknowledgements: The research leading to these results has received funding from "la Caixa" Foundation (LCF/PR/GN17/10300004). CCDC22 is a highly conserved protein that through its N-terminal part with COMMD proteins that take part in multiple processes including regulation of NF-kB signaling, copper export from the liver and sodium transport. Collectively, this study suggests that the CRISPR-Cas13a protein downregulated the ALK expression in the lung cancer cell. Materials and Methods: We recruited 32 families with pregnancy loss (n = 16 RPL cohort, n = 16 SA cohort) with normal karyotyping results in both parents and the fetus. We only included patients who had ≥10 histologically confirmed tubular adenomas and were tested with NGS panels for germline variants in years 2015-2020. Method: We selected genes from known biological pathways and then created polygenic risk scores (PRS) from available QTL data. Ownership Interest (stock, stock options, patent or other intellectual property); Modest; Icahn School of Medicine. N.P. Smirnova: None. P11.058.D Novel CNS malformations in De Barsy syndrome A Hannes S. Rossing: None. Bos5, Douglas Riegert-Johnson8, Sarah Mantia-Macklin6, Kai Muru1,2, Tiina Kahre1,2, Karin Hint1, Katrin Õunap1,2 1Department of Clinical Genetics, United Laboratories, Tartu University Hospital, Tartu, Estonia, 2Department of Clinical Genetics, Institute of Clinical Medicine, University of Tartu, Tartu, Estonia, 3Department of Medical Genetics, Oslo University Hospital, Oslo, Norway, 4National Resource Centre for Oral Health in Rare Disorders, Lovisenberg Diaconal Hospital, Oslo, Norway, 5Department of Genetics, University Medical Center Groningen, Groningen, Netherlands, 6Department of Clinical Genomics, Mayo Clinic, Jacksonville, FL, USA. There are around 16 variants of GSD, plus sub-variants, making about 25 in total. 2. Data were analysed using thematic analysis. Conclusions: Genetic variation at 11q14.1 was associated with Streptococcus gallolyticus colonization in saliva in African-admixed populations. Hoffman: None. P19.059.C Genome Diversity in Ukraine Taras K. P12.148.D Association of novel germline MLH1 in-frame deletion with uncommon isolated PMS2 loss in tumor tissue Gasper Klancar 1, Ana Blatnik2, Vida Stegel1, Olga Blatnik3, Primož Drev3, Barbara Gazić3, Mateja Krajc2, Srdjan Novakovic1 1Institute of Oncology, Division of Diagnostics, Department of Molecular Diagnostics, SI-1000 Ljubljana, Slovenia, 2Institute of Oncology Ljubljana, Cancer Genetics Clinic, Ljubljana, Slovenia, 3Institute of Oncology Ljubljana, Department of Pathology, Institute of Oncology Ljubljana, SI-1000 Ljubljana, Slovenia. Ashton: None. P11.116.B Novel SMARCA4 mutation identified in a patient with a mild phenotype of Coffin-Siris syndrome Beata Aleksiuniene 1,2, Loreta Cimbalistiene1,2, Algirdas Utkus1 1Department of Human and Medical Genetics, Institute of Biomedical Sciences, Faculty of Medicine, Vilnius University, Vilnius, Lithuania, 2Centre for Medical Genetics, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania. Nasvytiene: None. These genes encode proteins that act as transcription factors. Said: None. Cultured calvarial and long bone osteoblasts exhibit differences in differentiation pattern, dependent on mating scheme, age and skeletal site. Mena: None. We aim at evaluating the clinical utility of highly sensitive assessment of microsatellite instability (hs-MSI) in target tissues and non-invasive surrogates for the individualization of surveillance in LS carriers. The GPAP contains pseudonymised data from over 15,000 individuals and is a key resource for Solve-RD (, EJP-RD (and the ELIXIR RD Community (. Lipińska: None. Methods: We developed four minigene PAX6 constructs: i) exons 1 to 4, ii) exons 5a and 6, iii) exons 5 to 7 and iv) exons 8 to 11, respectively. Additional genetic (e.g., polygenic risk scores) and non-genetic risk factors can be integrated in CanRisk to perform gene-based associated analyses and model predictions. Conclusion: Eight GWAS loci that contribute to improve local clinical care, therapy, and genetic counseling. According to segregation-causative and gender-based incomplete penetrance analysis, a heterozygous variant and the fecundity in both parents, a sonographic screening by genetic predisposition. Additionally, based on the pilot genetic data analyses, we obtain and in the exome sequencing and comparative genomic hybridization of the whole exome, we found 129 and 112 variants respectively (AF1% frequency), adjusting the models for gender, age, and the first two principal components of genetic variation. Introduction: Intrauterine growth restriction (IUGR) is a condition in which the growth rate of the fetus during pregnancy is less than normal, being the second leading cause of perinatal mortality. P15.045.A Development of a novel, instrument-free, single-cell RNA sequencing technology (PIPseq) and its application to drug pathway discovery in lung cancerIain Clark1, Christopher D'Amato2, Ahmad Osman2, Sruti Pandey2, Yi Xue2, Aaron May-Chang2, Robert Meltzer2, Sepehr Kiani2, Kristina Fontanez 2, Adam Abate1 1UC Berkeley, Berkeley, CA, USA, 2Fluent BioSciences, Watertown, MA, USA, 3University of California, San Francisco, San Francisco, CA, USA. T7SGR437, GLD17/00282, FPU17/00361. The PRS and MR results are then combined to create an overall pathway PRS, validated in an independent sample. Based on these findings, we suggest that effective, equitable provision of remote counselling will require an infrastructure able to support video/counselling, sharing of clinical resources and with a robust counselling, sharing of clinical resources and connect with a wide range of individuals. In the second part of the conference, we selected 14 genes that were recurrently affected by breaks (FDR 0.5% were considered and filtered by quality and functional impact. According to NCCN guidelines, definitive LS diagnosis requires identification of germline pathogenic variant (PV) in one of the MMR genes. Targeted sequencing of the remaining exons was performed in cases where only one heterozygous pathogenic variant was found in exon 7. We postulated that longitudinal changes in microRNAs could be a signature of psychotic transition. Furthermore, phenotypic variations between OrthoVars from mouse and C. ES is a powerful and accurate method for the identification of causative variants in prenatal; trio sequencing reduces the turnaround time and likely increases the diagnostic yield. Callewaert: None. Systematic review Talia Yolanda Marroquin 1, Sandra Guauque-Olarte2 1Universidad Cooperativa de Colombia, Pasto, Colombia, 2Universidad Cooperativa de Colombia, Pasto, Colombia. While the variant SOX4Glu27* leads to a premature stop codon, the variant in the functional domains, SOX4Arg61Gln shows an exchange of an amino acid that is highly conserved in the HMG box of several proteins. Youssef: None. M., Finelli, R.H. Mutations in the cardiac poly purine gene SCRIB are associated with spinabifida. Passon: None. Also, there was limited phenotype data in fifth pregnancy to explain the cardiac anomaly. Ciuffreda: None. Our studies suggest that the predictive accuracies of psychiatric and neurological disordersClara Albiñana, Florian Privé, Esben Agerbo, ISPYCH-Broad Consortium, Preben B. R.A. Husain: None. Somatic mosaicism for pathogenic P4HB has already been described in one case. Neuberg: None. Bladder Cancer detection test which measures the levels of five target mRNAs (ABL1, CRH, IGF2, UPK1B, ANXA10) by RT-PCR and UroVysion Bladder Cancer Kit which is designed to detect aneuploidy for chromosomes 3, 7, 17 and loss of the 9p21 locus by FISH. Cartwright: None. P09.111.D Re-weighting hundreds of polygenic risk scores improves the prediction of psychiatric traits. Sequencing revealed a novel homozygous stop variant in exon 3 while two recessive genetic variants of SNP rs1107946 and rs1800012) within the COL1A1 gene, an important regulator of fibril assembly in tendons, have previously been associated with sports-related musculoskeletal soft-tissue (MSST) injuries. In addition to the core registry, ILIAD will include thematic sub-registries of patients with biologically proven monogenic or genomic (chromosomal) diagnoses, under the supervision of ERN-based curation teams. Ladoire: None. P08.078.D Expanding the spectrum of WAC-related intellectual disability to include 7 novel variants and a patient with congenital heart disease Rita Quental 1, Daniel Gonçalves2, João Parente Freixo3, Miguel Leão1 1Medical Genetics Service, São João University Hospital Centre, Porto, Portugal, 2Pediatrics Service, São João University Hospital Centre, Porto, Portugal, 3CGPP-IBMC, University of Porto, Porto, Portugal. In addition, normal karyotype was identified in all affected members. P04.037.B A novel c.671_682del NCSTN variant in a family with Hidradenitis SuppurativaNikolai P. Methylation calling was performed using the nanopype pipeline. This report expands the mutational spectrum of Alkuraya-Kucinskas syndrome and emphasizes its importance as a differential diagnosis of a severe cerebral pattern mimicking tubulinopathies (Cabet et. The proband, a 40-year-old female, began to show a progressive deafness since she was 17 years old. The details of their symptoms are presented in the Table. The additional material in the distal extremity of the chromosome 16 was difficult to identify by RHG banding. Antonova: None. Changes of HOX genes expression are associated with altered endometrium development. P16.030.A Translational diagnostics program: an in-house pipeline to validate genetic variants in children with undiagnosed and rare diseases Jordi Pijuan 1, Maria Rodríguez-Sanz1, Daniel Natera-de Benito2, Anna Altisent1, Carlos Ortez2,3, Raül Benítez4, Andrés Nascimento2,3, Janet Hoenicka1,3, Francesc Palau1,3,5 1Laboratory of Neurogenetics and Molecular Medicine – IPER, Institut de Recerca Sant Joan de Déu, Barcelona, Spain, 2Neuromuscular Unit, Department of Pediatric Neurology, Hospital Sant Joan de Déu, Barcelona, Spain, 3Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Barcelona, Spain, 4Automatic Control Department and Biomedical Engineering Research Center, Universitat Politècnica de Catalunya, Barcelona, Spain, 5Department of Genetic Medicine – IPER, Hospital Sant Joan de Déu and Hospital Clinic University of Barcelona, Barcelona, Spain. Materials and Methods: Blood samples have been collected from 30 PD and 30 age and sex-matched controls. Introduction: Osteosarcoma is the most common bone tumor in children and young adults. Pais: None. Tenorio: None. The results were filtered by frequency, impact region and gene function. Gustincich: None. Verbenko, Anastasiya A. Further studies are called for in order to determine the yield of prenatal ES in this setting. As a result both siblings, now 2 and 4 years old, show spastic tetraparesis, seizures, hydrocephalus, dysphagia, respiratory problems and cortical blindness. Introduction: Many genetic diseases are mapped to structurally complex loci. Acknowledgement: This study was supported by PCE grant "Testing small molecule targeting mitogen activated protein kinases: Successes, challenges and opportunities in triple negative breast cancer systems- ORIENT". In addition to providing a diagnosis, and a low recurrence risk for future pregnancies, this result is associated with a risk of cancer, most notably for retinoblastoma, osteosarcoma and other tumours requiring life-long surveillance. However, the predictive value of alcohol consumption explained by genetic risk score. Jamieson: None. Sensitivity to detect SNVs and INDELs with over 10% heteroplasmy was 100%. Investigating the "dark" genome and utilizing Phenomizer for diagnostic assistance are highlighted to identify clinically-relevant variants in unsolved cases/families. Centeno-Ramirez4, Xavier Godron1, Chia-Lin Wei2 1DNA Script, LE KREMLIN BICETRE, France, 2The Jackson Laboratory for Genomic Medicine, Farmington, CT, USA, 3Autonomous University of Zacatecas, Zacatecas, Mexico, 4Zacatecas State Health Services, Zacatecas, Mexico. P16.021.D Virtual genetic assessments for neonatal intensive care unit patients Demetra Georgiou 1,2, Libuse Pazderova1, Harry Leitch2, Emanuel Curekan1, Teena Ferguson1, Jan Cobben2 1Imperial College Healthcare NHS Trust, London, United Kingdom, 2North West Thames Regional Genetics Service, London, United Kingdom. Valenzuela Palafoll: None. Interestingly, patients with copy-number gains in 17p11.2 not including RAI1 and a DD phenotype often receive a prenatal diagnosis. Conclusion: Ongoing experiments on patient-derived neurons might be a future platform for personal treatment of diseases with a broad spectrum of mutation. ElGhazali: None. NGS techniques integrated with MLPA have largely overcome RNA-based techniques that are faster and with high yield, but do not detect splicing defects. Pharmacogenetic testing can be a good approach to move a more personalized approach and to improve disease management. P11.076.B Luscan-Lumish Syndrome, a fatal disease Susana García-Linares 1, Margarita Martínez-Atienza2, Irene Sofía Machado-Casas1, Antonio Emilio Jerez-Calero1, Susana Pedrinaci-Rodríguez2, María Luz Bellido-Díaz2, Matías Pérez-Sánchez2 1Hospital Universitario Clínico San Cecilio, Granada, Spain, 2Hospital Universitario Virgen de las Nieves, Granada, Spain. P23.031.C Healthcare professionals' perspectives and experiences with cases of nondisclosure of genetic information to relatives Anica Phillips 1, Danya F. Ezquerra-Zabicaray: None. PGT was not possible for 14 couples, mostly because the causative variant was not identified or of unknown significance. Introduction: Mitochondrial Membrane Protein-Associated Neurodegeneration (MPAN) is one of the major forms of NBIA, with an estimated incidence of 1/1,000,000 (less than 600 cases are described in the literature). Brazdziunaite: None. The majority of individuals with TBRS are healthy, however the bibliography reports possible complications of behavioural/psychiatric issues, kyphoscoliosis, febrile seizures, cardiac anomalies, hypotonia and/or joint hypermobility, and possibility of haematological malignancy. Constitutional MisMatch Repair Deficiency (CMMRD) is a rare and devastating childhood-onset cancer predisposition syndrome caused by biallelic mutations in MisMatch Repair (MMR) genes. Here, we present a de novo duplication of 8p23.1 found at a prenatal cytogenetic diagnosis. We report a newborn of healthy nonconsanguineous parents, born after a pregnancy complicated with polyhydramnios, at 36 weeks, by urgent cesarean delivery. Introduction: Parkinson's disease (PD) is a progressive neurodegenerative disorder with the clinical characteristics of bradykinesia, tremor and rigidity. We have asked Healthcare Professionals in UK clinical genetics services to provide insight into their experience of nondisclosure. Vich-Vila: None. Bodega: None. This variant was not reported in the literature in HCM cases nor described in the Human Genome Mutation Database (HGMD). 1Genetics Unit, Hospital Universitario La Paz, IdiPAZ, Madrid, Spain, 2CIBERER, ISCIII, Madrid, Spain. 27 cases had non-diagnostic variants in MYBPC3, 48 in other sarcomeric genes and 10 cases, diagnosed with a cardiomyopathy post-mortem. D.A. Petukhova: None. Funding: Novo Nordisk Foundation (cbmr.ku.dk)(grant number NNF18CC0034900), TOK (NNF17OC0026848), HJ (NNF17SA0031406). Two other sporadic patients affected with isolated ectrodactyly of the feet carried microdeletions spanning less than 200 kb encompassing the limb-specific enhancers hs1467 (hg38: chrX:25013469-25013696 and chrX:11744737-111744820 (hg38) overlaying the ARX (aristaless-related homeobox) and ALG13 genes, respectively. Funding: A. Semerci Gündüz: None. Morrone: None. Funding: R01NS100178, R01NS105150, 7U01HG010606, R01NS105150, 7U01HG010606, NWO vidi 639.072.715, CVON 2011/B019, CVON 2017-20, ICIN.09.001, 01KL1802. A.V. Ponasenko: None. The knowledge gained might contribute to common treatment strategies for all aaRS-related neuropathies. P06.003.D Difficulties in diagnosing alpha-mannosidosis Gabriela Ceresek 1, Camelia Alkhzouz2,1, Vasilica Plaiasu3 1Children's Emergency Hospital, Cluj-Napoca, Romania, 2"Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania, 3INSMC "Alessandru Rusescu", Bucharest, Romania. Introduction: Alzheimer's disease (AD) is an irreversible, progressive brain disorder leading to dementia. In total, we identified 164 somatic variants, which were classified as pathogenic. Rodriguez-Jiménez: None. Olde Keizer2, Geert W. Methods: We generated fly models for four CMT-related aaRS by expressing two pathogenic mutations (one altering and one not affecting the enzymatic activity) using a modified GeneSwitchTM technology. Clinical exome sequencing revealed two heterozygote variants, c.1567-23_156722del and c.1703_1718+25del in the KATNB1 gene. Investigation of neurodevelopmental disorders may unravel protein networks, crucial for brain development. The also contained alterations in HLA genes, but also in the genes of metallothionein and apolipoprotein D. P23.044.D Standardised tool for documentation of rare genetic disease costs: development, contextualisation, translation, and validation of the Client Service Receipt InventoryClaudia C. Male androgenetic alopecia (AGA) has been implicated as a putative risk factor in severe COVID-19 based on high incidences of AGA in male hospitalised COVID-19 patients. Whole exome sequencing (WES) was proposed and performed on Illumina HiSeq platform. A distinctive syndromic form was reported with 'club feet', intellectual disability, ophthalmic dyspraxia and muscle atrophy (Wieckaer 1985). Knorre: None. Results: Detection rate was 13,5%: 28 in heterozygous and 7 in compound-heterozygous. Konecna: None. Muggenthaler1,4, Emma L. We used a human induced pluripotent stem cell (hiPSC) line in which the expression of a deactivated Cas9 fused to a KRAB repression domain (dCas9-KRAB) is induced upon doxycycline (Dox) treatment. We monitor the MDC-NP score as simplified and sensitive bedside screening tool for rapid identification of children with mitochondriopathies. Braz: None. Stieber: None. Instituto de Investigación Sanitaria La Fe,, Valencia, Spain. Bedeschi: None. Genetic data imputed using 1000 Genomes Project was used to perform genome-wide association studies (GWAS) following two different approaches, sex-interaction and sex-stratified analyses, and results obtained from each cohort were meta-analyzed. Results: The chromosomal microarray analysis revealed CNVs considered pathogenic in 43 (18.0%) of affected individuals, ranging from 3.7 kb to 16.9 Mb in size. Proximal interactions between TLX2 and other factors were observed during enteric neurogenesis, including CHD7, CHD8, BRD4, NACC1, were identified. Genes variants were carried out by using PCR-RFLP and allele-specific PCR, respectively. The number of described patients with STAG1 variants is very small thus it's phenotypic spectrum may be wider than currently described.Funding: Estonian Research Council grant PRG471, MOBTP175 K. Partial trisomy 13q is an uncommon chromosomal abnormality with a variable phenotypic expression, but in most cases less severe than those found in complete trisomy 13. A.K. Alieva: None. Barcoded amplicons were pooled together for the preparation of a SMRTbell library, which was sequenced on the PacBio Sequel II and IIe Systems. In UK Biobank, 4733G>A and compound heterozygosity with 4925G>A were associated with a lower hazard ratio for CAD (9% [95%CI:7-11%] and 12% [95%CI:716%] (both pT (p.Asn219Tyr) of the MUT gene was detected. A limited number of genes differentially expressed in the affected patient affect pathways potentially relevant for the observed phenotype divergence. Introduction: Severe tinnitus is a heterogeneous condition reported in 1% of the population, showing a significant heritability. Martínez-Rubio: None. Schwarz: None. E.D. Teplyakova: None. Valkovicova: None. Bioinformatic analysis was performed with the GATKv4 and CoNVaDING for CNV analysis, using the GRCh38 reference genome. Tjitske Kleefstra: None. Introduction: Families with several cases affected by CL/P can provide evidence for etiological factors. Abstract: Syndromic causes of oral clefts are rare disorders that can present along with congenital malformations or craniofacial anomalies e.g.: isolated cleft palate and chondrodysplasia, esophageal atresia (type III, cleft palate and ear pits. By combining exome and RNA sequencing, we provide evidence that MYH3:c.1581+1G>A variant, previously reported in association with CPSFS1 (PMID:29805041) is likely associated with a dominant predisposition to CPSFS1. Furlano: None. Introduction: Glioblastoma (GBM) represents significant public health problem. Background: The diagnosis of developmental delay, epilepsy and microcephaly is complicated by the variability of the phenotypic manifestations. Ravoet: None. This study is funded by the National Science Foundation of Sri Lanka (NSF/SCH/2016/04) J.T. Kotelawala: None. Also, preliminary data from a large dataset indicate the presence of a statistically significant preponderance of neurological symptoms in heterozygous patients. Introduction: There are many clinically important genes "dark" regions of the human genome. The collection includes peripheral blood samples from pregnant women; whole blood, serum, plasma, buffy coat, and urine were collected during pregnancy, and placenta and umbilical cord blood samples were collected during labor. Martínez Bugallo: None. T.S. Ajanci: None. Hearing loss (HL) is the most common sensory disorder worldwide. These results indicate that CSA should be used when making a decision to initiate treatment. Limongelli: None. Introduction: Subtelomeric chromosomal changes are rare. Introduction: Alzheimer's disease (AD) is the most common neurodegenerative brain disease affecting millions worldwide. Almaguer-Mederos 1, Suzana Gispert2, Dennis Almaguer-Gotay1, Raúl Aguilera-Rodríguez1, Yanetza González-Zaldívar1, Yaimé Vázquez-Mojena1, Dany Cuello-Almarales1, Daniel O. AKT3 is one of 3 closely related serine/threonine-protein kinases (AKT1,AKT2 and AKT3) which regulate processes including metabolism, proliferation, cell survival, growth and angiogenesis. Lupski5,15,16, Nebal W. Xiong: None. At physical examination both showed round face, well-defined eyebrows, bulbous nose with anteverted nostrils, disharmonic short stature with short limbs, relative macrocephaly, and brachydactyly; hand camptodactyly was detected during childhood in the father and in the child at 4 years of age. P08.037.C THUMPD1 is a new cause of syndromic intellectual developmental disorder Martin Broly 1, Bertrand Isidor1,2, Thomas Besnard1,2, Declan O'Rourke3, Julia Baptista4,5, Sian Ellard4,5, Mohammed Almannai6, Hashem Mais Omar7, Ferdous Abdulwahab7, Hanan Shamseldin7, Saeed Al-Tala8, Fowzan S Alkuraya7,9, Alleen Leon10, R.L.F. van Loon11, Alessandra Ferlini12, Mariabeatrice Sanchini12, Stefania Bigoni12, Mitchell O'Connell13, Bogdan Polevoda13, Kamel Awayda13, Stéphane Bézieau1,2, Benjamin Cogné1,2 1Service de Génétique Médicale, CHU de Nantes, Nantes, France, 2Université de Nantes, CNRS, INSERM, l'institut du thorax, Nantes, France, 3Department of Neurology, Children's Health Ireland at Temple Street, Dublin, Ireland, 4Exeter Genomics Laboratory, Royal Devon and Exeter NHS Foundation Trust, Exeter, United Kingdom, 5Institute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter, United Kingdom, 6Section of Medical Genetics, Children's Hospital, King Fahad Medical City, Riyadh, Saudi Arabia, 7Department of Translational Genomics, Center for Genomics Medicine, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia, 8Pediatrics Department, Armed Forces Hospital, Khamis Mushait, Saudi Arabia, 9College of Medicine, Alfaisal University, Riyadh, Saudi Arabia, 10Research & Innovation (R&I Genetics) Srl, Genetic Laboratory, Padua, Italy, 11Department of Genetics, University of Utrecht, University Medical Center Utrecht, Utrecht, Netherlands, 12Medical Genetics Unit, Department of Medical Sciences, University of Ferrara, Ferrara, Italy, 13Department of Biochemistry and Biophysics, Center for RNA Biology, University of Rochester, Rochester, NY, USA. Belen5, Neslihan Karakurt6, Ozgur Cogulu1, Ferda Ozkinay1, Tahir Atik1 1Ege University Faculty of Medicine, Izmir, Turkey, 2Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey, 3Uludag University Faculty of Medicine, Bursa, Turkey, 4Erciyes University Faculty of Medicine, Kayseri, Turkey, 5Başkent University Faculty of Medicine, Ankara, Turkey, 6Sancaktepe Prof. Introduction: The identification of the short (p) arm of chromosome 8 is a rare syndrome. We find that Random Forest or regression are globally the best performing methods. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Modest; Medical Genetics Research Fellowship Program. of Clinical Genetics, Aarhus University Hospital, Aarhus N, Denmark, 2Center for Prenatal Diagnostics, Aarhus University, Aarhus, Denmark, 3Defactum - Public Health & Health Services Research, Aarhus, Denmark. Existing methods for identifying mix-ups are limited to datasets in which additional omics data (e.g. gene expression) is available. D'Alessandro: None. Child 1 was born small for gestational age and presents with microcephaly, speech delay, ectopic renal tissue and dysmorphic features including epicanthal folds, a broad nasal bridge and upslanting palpebral fissures. Genome-wide association studies (GWAS) of ischemic stroke (IS) commonly aim to identify genetic variants associated with IS risk by applying a case-control design. Piscia: None. Shetty2, Anju Shukla1, Katta M. Employment (full or part-time); Modest; enGenome srl. This is of particular concern where a precise epilepsy molecular diagnosis informs drug choice and misdiagnosis may have devastating and lethal consequences. Introduction: Trichorhinophalangeal syndrome type I (TRPS1) is a rare genetic disorder characterized by distinctive facial features (bulbous pear-shaped nose), ectodermal anomalies (sparse hair, dental anomalies, dystrophic nails), and skeletal findings (brachydactyly, cone-shaped epiphyses of phalanges, short stature). Material and methods: Paraffin-embedded tumor samples obtained from 96 patients diagnosed with ovarian cancer using a customized panel containing ten genes (BRCA1, BRCA2, BRIP1, MLH1, MSH2, MSH6, PMS2, RAD51C, RAD51D and TP53). Börklü-Yücel: None. Results: We identified thirteen subjects carrying 13 variants in 7 monogenic obesity genes (LEPR, PCSK1, MC4R, NTRK2, POMC, SH2B1 and SIM1) of which 4 predicted (likely) pathogenic through ACMG criteria. Pichon: None. Mazel: None. Yurkina1, Maria G. Hearing loss was pre-lingual in 78% of cases and profound in 70%. Cancer cell lines are good models for genomic mechanisms and testing for possible drugs. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Modest; São Paulo Research Foundation. P10.047.C Prediction of Parkinson's disease risk from a polygenic profile with established risk factors Ian Cassar1, Andreas Hadjisavvas2,3, Maria A. P19.017.A Using genetics to understand the biological and mechanistic link between infectious susceptibility to EBV infection Marisa D. Genetic causes remain unexplained for 20% to 30% of patients with globozoospermia suggesting that this phenotype is likely genetically heterogeneous. Only eight cases of somatic DMD mosaicism are published to date. Garrett: None. Possible mechanisms to explain these chromosomal abnormalities will be discussed in detail. To identify protein variants, we performed exome sequencing on 29 individuals from the NSCLC study, created personalized mass spectrometry search libraries for each individual, and identified 464 protein variants. In two patients FBN1 mutations were found (c.8051+2T>A and p.Arg516Ter). Vabres: None. Golubickaite: None.

Grob: None. P19.047.C Association between genes LPL Ser447Ter and FTO rs9939609 polymorphisms with obesity in children and adolescents Alaa Hashim Abd Ali 1,2, Olga Vladimirovna Bocharova3, Tatiana Pavlovna Shkurat4 1South Federal University, Academy of Biology and Biotechnology, Rostov-on-Don, Rostov, Russian Federation, 2Al-Furat Al-Awsat Technical University, College of Health and Medical Techniques, Department of Medical Laboratory Techniques, Kufa, Iraq, 3Rostov State Medical University, Rostov-on-Don, Russian Federation, 4South Federal University, Academy of Biology and Biotechnology, Rostov-on-Don, Russia, Russian Federation. P05.033.C Diagnostic yield of cardiac gene panel testing in inherited cardiac conditions patients in the Republic of Ireland Jane L. Moreover a single case of Leukodystrophy was identified with null NOTCH3 mutation unexpectedly acting in recessive heredity. Conclusions: By using our approach, we were able to describe the first case of USH syndrome, its incidence and distribution in Sardinia. Jakubowska: None. DNA from the proband was subjected to genome sequencing and bioinformatics analysis. CIHR, FRQS, National Ataxia Foundation S. Liparulo: None. P02.061.B Metastasis suppressor 1 as a novel candidate gene for inherited retinal dystrophy Solomon Merepa 1, Suzanne Broadgate1, Jing Yu1, Sumathi Sekaran1, Susan Downes1,2, Stephanie Halford1, United Kingdom Inherited Retinal Dystrophy Consortium (UKIRDC) 1Nuffield Laboratory of Ophthalmology, Department of Clinical Neuroscience, University of Oxford, Oxford, United Kingdom, 2Oxford Eye Hospital, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom. Heide13, RC. Case report An infant boy presented with progressive corneal clouding at the Department of Ophthalmology. Results: A pathologic CAG repeat expansion in ATXN7 was found to cause SCA7 with clear maternal anticipation in the ADHA family. These endemic variants will become a valuable resource for designing future population and clinical studies, help address questions about ancestry and admixture, and will fill a missing place in the puzzle characterizing human population diversity in Eastern Europe. Spitali: None. Prognosis for outcome of the disease and treatment are associated with histopathology of the tumor. Bánfai: None. Above and beyond a general positive attitude towards sharing, respondents were clear when expressing their preferences between potential sharing recipients, "My Medical Doctor" (60%) as opposed to "For Profit Researcher" (38%). Hatirnaz Ng: None. Girós: None. Milovanova2, Kseniya V. Ordonez: A. H.V. Duyvenvoorde: None. Conclusion: Prenatal and postnatal lymphatic problems are common in NS and Noonan-like syndrome patients. Obesity has a highly complex genetic architecture, making it difficult to understand the underlying disease mechanisms, despite the large number of loci discovered via genome-wide association studies (GWAS). Our results therefore indicate lack of correlation between DMD exon 2 duplication splicing choices and DMD phenotype. The result of the segregation analysis strengthened the mutations in trans.This study was supported by KTIA_13_NAP-A-III/6; KTIA_NAP and with FIKP program. P17.054.A Penetrance estimation of SORL1 loss-of-function variants using a family-based strategy adjusted on APOE genotypes suggest a non-monogenic inheritance Catherine Schramm 1, Camille Charbonnier1, Aline Zaréa2, David Wallon2, Morgane Lacour2, CNRMAJ collaborators, Flora Alarcon3, Emmanuelle Génin4, Dominique Campion1, Grégory Nuel5, Gaël Nicolas1 1Normandie Univ, UNIROUEN, Inserm U1245 and Rouen University Hospital, Department of Genetics and CNR-MAJ, Rouen, France, 2Normandie Univ, UNIROUEN, Inserm U1245 and Rouen University Hospital, Department of Neurology and CNR-MAJ, Rouen, France, 3CNRS 8145-MAP5, Paris, France, 4Inserm U1078, Brest, France, 5CNRS 8001 - LPSM, Paris, France. LOH was evaluated in 3 tumors so far: two presented absence of LOH for variants in XPC and ERCC2 and one presented LOH for a variant in SLX4. Takeda: None. Richthammer: None. Thorsteinsson 1, Vigdis Stefansdottir2, Sigridur Thorisdottir2, Thor Eysteinsson1, Jon J. In CYP3A5 we found the highest number (87.5%) of inactive alleles. Parental studies confirmed this deletion occurred de novo. Materials and methods: To assess NAPs, we developed or acquired through collaboration single-gene heterozygous knockout mice, representing 20 unique genes of the 16p11.2 locus. Palvadeau: None. Le Goff: None. The newly composed MDC-NP-tool, in contrast, exhibited a significantly higher sensitivity (0.83; 0.65-0.93) and a specificity of 0.96 (0.92-0.98). Size and coordinates of copy number alterations detected by OGM and CMA were highly concordant. P04.064.A Systematic analysis of non-coding de novo mutations from whole genome sequence data of triads with non-syndromic cleft lip with/without cleft palate Hanna K. Poulsen: None. We conducted a genome-wide quantity trait locus analysis to probe genetic variants linked to levels of cell-associated (CA)-HIV-1 DNA, CA-HIV-1 RNA and RNA:DNA ratio in whole blood CD4+ T cells from a HIV-1 patient cohort (207 Caucasians) under long-term suppressive cART (median 6.6 years). Stewart: None. Besides new attempts to identify a missing pathogenic allele, functional studies may also clarify their causative role and, ultimately, provide a definitive diagnosis. Maly: B. However, the evolutionary driving forces establishing this trend are still unknown. This arginine residue was also conserved in zebrafish. The fetus in case 2 presented hydrocephalus. The growing understanding that social distancing is the best way to reduce the chance of COVID-19 contagion, combined with the long-term lockdowns, forced the entire healthcare system to adapt new healthcare methods. We currently evaluate DNA extracted from FFPE-tissue. Materials and Methods: The custom panel consisting of 116 variants in CFTR, PAH, SERPINA1, and GJB2 genes was designed and tested on two population-based cohorts that included 1858 ESSE-Ivanovo and 1244 ESSE-Vologda participants. Results: Five heterozygous missense mutations candidate as genetic modifiers passed our filtering steps including variants with MAF less than 0.05 and eVai pathogenicity score at least 3.5, associated with clinical conditions sharing at least 4 Human Phenotype Ontology terms with the patient. So far, mutations in the first and third third of the GLI3 gene have been associated with GCPS while mutations in the second third of GLI3 have been associated with PHS. Further techniques are required for identification like molecular karyotyping or different methods of molecular cytogenetic. Ahmad: None. Brouillard: None. Result: Two compound heterozygous variants in trans position were found: pathogenic variant NM_000051.3(ATM):c.3214G>T;.Glu1072Ter (inherited from father) and variant of unknown significance NM_000051.3(ATM):c.8710G>C ;Glu2904Gln; (inherited from mother). Results: The study population consisted of 267 patients, with a median age of 18 years (IQR: 9-34). W.S. Kerstjens-Frederikse: None. Tulasne: None. Two pairs of centrioles might disturb the segregation of chromosomes, causing aneuploidy. Results: 86 and 140 loci provided evidence of genetic colocalization with adipose and brain-derived gene expression respectively, suggesting that the genetic variants which influence BMI at these loci also influence proximal gene expression in these tissues. We compared two tests: FISH test UroVysion Bladder Cancer Kit routinely used in our laboratory and mRNA-based urinary marker test Xpert®Bladder Cancer Detection. Introduction: Several genetic diseases are associated with cytosine methylation (5'-mC) of CpG dinucleotides. The aCGH analysis revealed additional CNV represented as pathological microduplication occurring at the 7q31.1 cytoregion (513 kb, including IMMP2L and LRRN3 genes). After IGV and selection step, 58 genetic variants in 52 different candidate genes were validated by Sanger sequencing (Table 1). Shadrina1, Elizaveta E. J.L. Murphy: None. Salivetto: None. Introduction: The hypothalamus-pituitary-adrenal axis mediates the neuroendocrine response to stress. P17.015.B Nucleosome positioning based identification of tissue contributions in cell-free DNA Sebastian Röner 1,2, Martin Kircher1,2 1Charité Universitätsmedizin Berlin, Berlin, Germany, 2Berlin Institute of Health (BIH), Berlin, Germany. Usdin: None. All studied patients were descending from consanguineous families and most of the characterized mutations were found in a homozygous state. B.P.C. van de Warrenburg: None. Most of the HNSCC cell lines reported do not come from the primary tumour site and its molecular characterization is not available. Lei, Y., Zhu, H., Duhon, C., Yang, W., Ross, M. Duplomb: None. Fasham 1, Joseph S. A mechanism of functional consequences of the detected variants combination is proposed to be accumulation of several defects, violations of blood/retina barrier, as well as diminishing of the ciliary transporting potential. Additionally, MLPA analysis was used to confirm presence of CNVs. Results: A novel RHO-mutation (c.803A>G, p.Tyr268Cys) was identified in 5 patients with adCSNB. 113 formalin-fixed paraffin embedded (FFPE) tumor samples were collected from patients with HNSCC (oropharynx: 65 (57.89%); larynx: 48 (42.11%)). This deletion is to our knowledge of yet undescribed extent. Up to 6% of the risk variant frequency was observed in our cohort, highlighting the prevalence of high-cost ADRs. More studies are needed to understand the impact on total cost of care. Inspection of our model revealed that for patients with ID, comorbid abnormal (lower) muscle tone positively correlated with the prediction for a conclusive WES diagnosis, whereas autism was negatively associated with a molecular diagnosis. P02.039.D RPE65-related retinal dystrophy: mutational and phenotypic spectrum in 45 affected patients Rosario Lopez-Rodriguez 1, Esther Lantero1, Fiona Blanco-Kelly1, Almudena Avila-Fernandez1, Inmaculada Martin Merida1, Marta del Pozo-Valero1, Irene Perea-Romero1, Olga Zurita1, Belén Jiménez-Rolando2, Saoud Tahsin Swafiri1, Rosa Riveiro-Alvarez1, María José Trujillo-Tiebas1, Ester Carreño Salas2, Blanca García-Sandoval2, Marta Corton1, Carmen Ayuso1 1Department of Genetics & Genomics, Instituto de Investigación Sanitaria-Fundación Jiménez Díaz University Hospital- Universidad Autónoma de Madrid (IIS-FJD, UAM), Centre for Biomedical Network Research on Rare Diseases (CIBERER), Madrid, Spain, 2Department of Ophthalmology, Fundación Jiménez Díaz University Hospital (FJD), Madrid, Spain. Results: Twelve articles were included in our analysis. Research using the NGS technique facilitates and accelerates the diagnosis of patients with delayed psychomotor and speech development, ASD and dysmorphic features. This syndrome starts with a genetic mutation in a multipotent hematopoietic progenitor cell.This clinical report is about a female, 82 years old, without relevant personal history, who has normochromic normocytic anemia with hemoglobin of 8.2 g/dL. However, the biological mechanism remains unclear. Total body X-rays and trio Clinical Exome Sequencing (CES) were requested. Methods: Illumina 850k® chips were used to perform CMA in 2000 affected individual for different clinical reasons at Ankara City Hospital in 2019-2020. We propose the use of our ID panel as first tier diagnosis in unexplained ID patients. hiPSCs were differentiated into cardiomyocytes resulting in a homogeneous population of mature beating cells within 30 days. Peixoto: None. This case illustrates the diagnostic utility of WES data re-analysis and importance of periodically revisiting uninformative results against growing evidence base for genetic causes of disease. Introduction: Individuals with mosaic pathogenic variants in the FBN1 gene are mainly described in the course of familial screening. Introduction: GDD is defined as a significant delay in 2 of the major developmental domains (gross/fine motor,speech/language, cognition, social/personal, and activities of daily living), although most affected patients have impairment evident in all 5 of the domains. Analyzes of protein expression and evaluation of loss of heterozygosity (LOH) in tumor tissue are being performed in cases with pathogenic variants. Blanco Pérez: None. P12.077.A Development of APC-specific ACMG/AMP variant classification guidelines Isabel Spier 1,2, Xiaoyu Sherry Yin3,4, John-Paul Plazzer3, Andreas Laner5, Ian M. Gene expression changes in T and B cells are considered to be the main initiator of disease pathology. Conclusions: This case report suggest to carry out an accurate funduscopic examination in order to highlight alterations of the optic disc in patients with RASopathies to obtain a precocious diagnosis of optic nerve involvement. We shall present UK NHS data on analysis of >1500 BRCA variants to exemplify our proposed approach to graded quantitative application of ACMG evidence item PS4, namely use of variant-level case control data. Materials and Methods: Following informed consent, exome sequencing and linkage analysis were undertaken on four affected and four unaffected siblings. Other possibilities of segregation are possible and can give non-viable fetus which explained the spontaneous abortions.The recurrence risk for DS due to an inherited translocation is difficult to evaluate and it is about 10%. Miramar: None. Results: ONS identified all pathogenic CNVs with detection time inversely proportional to size and allelic fraction. Genotyping was performed using fragment analysis by capillary electrophoresis. Results: 4733G>A (38.3% carriers) is the second strongest genetic factor besides the CNV already explaining 10% of Lp(a) variance. R.W. Benz: A. Riboli: None. Kozhamkulov: None. The variant classification followed the American College of Medical Genetics and Genomics (ACMG) guidelines. Materials and Methods: 49 female patients with NSCLC were included in study. Materials and Methods: Fifty-six healthy Kuwaitis and 113 Kuwaiti MS patients were exome sequenced on Illumina's HiSeq2000, and 404 healthy Arab control exomes from public databases were used. Results: Molecular genetic analysis identified two previously unreported heterozygous cis-variants c.236A>C and c.251T>G in MMP13 in a Czech boy suspected with metaphyseal anadysplasia, type 1. I.V. Bure: A. Long-insert genome and Sanger sequencing were performed for identifying structural variants in their responsible for the clinical phenotype. Diallo: A. Diderich1, Malgorzata I. A genetic result was achieved in a mean time of 30,8 days. P11.019.A 11p15 imprinting defects and phenotype expression in 12 patients with Beckwith-Wiedemann syndrome Ivona Sansovic, Ljubica Boban, Mijana Kero, Ingeborg Barisic Children's Hospital Zagreb, Scientific Centre of Excellence for Reproductive and Regenerative Medicine (CERRM), University of Zagreb School of Medicine, Zagreb, Croatia. Acknowlegdments: Fondation Courtois, FRQS J. Different cell types have different levels of mosaicism. Sánchez: None. Chamoieva: None. Pasterkamp: None. Cantalupo: None. B.P. Alter: None. Affected patients show a distinct phenotype that includes microcephaly, mild short stature and intellectual disability of variable degree. Using APOB as an exemplar, the top ten ranked genes identified to have the most comparable quantitative trait fingerprint to APOB are: PCSK9, GIGYF1, NPC1L1, ZNF229, ANGPTL3, RRBP1, ACVR1, SLC4A1, APOC3 and PDE3B. Vandenberghe: None. Pié: None. Very rare FRAS1:p.E296K and C2CD3:p.A2041V were found in daughters but not father. Altena: None. Nitschke: None. Among wild-type germline patients, a somatic mutation in ATM and BRCA1/2 and was observed in two and three patients, respectively. Bertola23, Alexander A. List of CFTR variants in CF patients from Ugra CFTR variant calling (HGVS; legacy) type of variant n = 117 % 1 c.1521_1523delCTT ([delta]F508) del w/o frameshift 57 48.7 2 c.54-5940_273+10250del21kb (CFTRdele2,3) large rearrangement 6 5.1 3 c.1545_1546delTA (1677delTA) del w/frameshift 6 5.1 4 c.274G>A (E92K) missense; splicing defect 5 4.3 5 c.3196C>T (R1066C) missense 4 3.4 6 c.3909C>G (N1303K) missense 3 2.6 7 c.412_413insACT (L138ins) ins w/o frameshift 2 1.7 8 c.1397C>G (S466X)* nonsense 2 1.7 9 c.1399C>T (R1070Q)* missense 2 1.7 10 c.3209G>A (L467F) VUCS 2 1.7 11-38 28 variants (each 0,9%) all 28 23.9 M. Materials and Methods: Family with three recurrent stillbirths and a newborn that deceased a few days after birth. Results: Based on the principle of do no harm, it is necessary to take into account the damage that may arise for both the child and the parents. Muto: None. These cases suggest the clinical relevance of drug interactions in patient harboring SCN5A heterozygous mutations. Introduction: Hemophilia B is an X-linked bleeding disorder caused by molecular defects in the Factor IX gene (F9), leading to either deficiency or functional abnormality of Factor IX. Pescia: A. In other cases, the genome is heterozygous, often from two spermatozoa. The ROC curve analysis showed that miR-21-3p can distinguish laryngeal tumor from normal tissue (AUC = 0.816; 95% CI:0.720-0.917;p = 1.76.10-6) with sensitivity of 84.2% and specificity of 73.7% whereas miR-210-3p did not. Results: Pathogenic and likely pathogenic variants were identified in 84 genes in 107 patients (107/501, 21,4%). Herein, we present two different syndromic craniosynostosis in the same family. Conclusion: The results of this study are compatible with current literature. Grant Sarepta Therapeutics (CPMS project). Introduction: With the implementation of the NGS sequencing, the process of diagnosing inherited metabolic diseases (IMD) has undergone a substantial change. McTague: None. Three unaffected sisters all inherited the variant. There was also a positive correlation with milk intake and diabetes. of Ophthalmology, Medical University of Silesia, Katowice, Poland, 3Center of Medical Genetics Genesis Sp. z o.o., Poznań, Poland. Demirel: None. Network analysis will be performed on this data. Furthermore, BioID results demonstrate that the germline p.R661P mutant retains similar interactors as that of wild-type FGFR1, while the double mutants share many with p.N546K, recapitulating the interactome of this activating mutant. Kubanov State Research Center for Dermatovenerology and Cosmetology of Russian Ministry of Health, Moscow, Russian Federation. Volakhava: None. This phenotype is reminiscent of the maternally-inherited Leber hereditary optic neuropathy (LHON), the existence of which has been described only very recently along with causative variants in NDUFS2 and DNAJC30, respectively. F9 variant analysis was performed from total genomic DNA by PCR followed either by SSCP and DNA sequencing or direct DNA sequencing. D.G.R. Evans: None. We describe here a new patient issued from non-consanguineous parents with SIDDT and epileptic encephalopathy. SERPINB6 (serpin family B member 6, also called protease inhibitor 6) was mapped to the DFNB91 locus in 2010 and causally associated with moderate-to-severe high-frequency hearing loss. Pennings: None. Twenty-four laboratories from 13 countries assessed the template (RR = 58.5%). Genetic origin is associated with pathogenic variants in MMP13 gene. During DNA Repair of UV-lesions, rDNA/RNAP1 are both reorganized within the nucleolus, namely, they migrate at the periphery of the nucleolus during DNA repair reactions and come back within the nucleolus after DNA repair completion. Consultant/Advisory Board; Modest; Regeneron Genetics Center. HTSeq (to count the number of reads transcripts), edgeR (count data were analyzed). Gunbin: None. These individuals presented with a progressive encephalopathy with various degrees of movement disorders, microcephaly, and epilepsy. Material and methods: Splicing effects were predicted using HSF3.1, MaxEntScan and SpliceAI. Fader Kaiser: None. Calame1, Zeynep Coban-Akdemir3, Jawid M. Clinical findings included resistant epilepsy, neurodevelopmental delay, neonatal diabetes, inguinal hernia, hydrocele testis, humoral immunodeficiency. P04.077.B lncRNA gene variants SPRR2C rs2291979 and LOC105375120 rs4724102 are associated with psoriasis Laimutis Kucinskas 1, Migle Anilionyte1, Vesta Kucinskiene2, Skaidra Valiukeviciene2 1Institute of Biological System and Genetic Research, LUHS, Kaunas, Lithuania, 2Department of Skin and Venereal Diseases, Lithuanian University of Health Sciences (LUHS), Kaunas, Lithuania. In mice sera, these bacteria significantly increased the expression of 25 genes or proteins belonging to apoptosis, TLR signalling, TGF-beta, inflammation, and angiogenesis pathways. When compared with E1, a significant decrease in ACTB_short (71% P = 0.0162), ACTB_medium (66% P = 0.0011) and ACTB_long (78% P = 0.0001) was observed. The project involves the extension of the list to the number of 800 blood samples. Babici: None. Tsuiko: None. The A allele (AA + GA) presence promoted a 1.5-fold decrease in TNF gene expression upon stimulation with IFN-γ compared to GG. Kastner: None. J.J. Jans: None. Novel therapeutic approaches to extending reproductive lifespan are likely to have wider effects on population health over prolonged fertility. Materials and methods: In our work, we assessed the association of the polymorphic variants STAT3 G>C (rs2293152), IL-10 -1082G>A (rs1800896) and IL-12B +1188A>C (rs3212227) genes with high-risk HPV infection among of women 30 years and older (104 women with HPV load more than 3 lg and 110 women without HPV). Ive: None. Wąsik-Szczepanek: None. The detected variant was found in proband's healthy mother. Eight double carriers (73%) had cancer: breast cancer (5 cases, 2 bilateral), melanoma (2 cases), urothelial cancer (2 cases), and colon, endometrial, prostate, squamous cell cancer, glioblastoma, gastric stromal tumor, and lymphoma (1 case each). Cuevas, Serafim Batzoglou, Asim Siddiqui, Omid C. Data on extracolonic manifestations of MAP is limited. Emich*: None. Cardaropoli: None. Leyden: None. Epilepsy is a complex disorder characterized by a predisposition to recurrent seizures that are caused by abnormal neuronal firing in the brain. Drev: None. Results: In three cancer patients with a clinical presentation highly suggestive of CMMRD, we excluded CMMRD and identified a constitutional heterozygous POLE PV. Strikingly, the rate for COVID-19 studies has been extremely high (99%). Association analysis was performed using SNPs (909) of the genes involved in tooth health (59 genes). Alasiri: None. In Study 4053-101, we demonstrated exon skipping and dystrophin restoration in all patients. M.F. Mattos: None. Discussion and conclusions: We report the 11th patient (sixth family) with confirmed MDST, and review the existing literature. This study was funded by the Ministry of Science and Higher Education of the Russian Federation №0852-2020-0028. Gjurkova: None. Feki: None. J.M. Collée: None. Materials and Methods: We analyzed the exons of BARD1, PRDM9, RCC1, and RECQL (plus 3'- and 5'- 25 flanking bases) of ~400 patients with ovarian cancer by targeted next-generation sequencing of 25 pooled DNA samples (16 individuals/pool, including several positive-control and duplicated samples). Parental origin of de novo NF1 deletions was determined in thirty trios and three duos using four intragenic and three extragenic microsatellites in the NF1 locus. P08.028.B Electrophysiological and proteomic investigations of an Ftsj1-deficient mouse model for intellectual disability Lars Jensen, Marian Baldus, Simone Venz, Heike Junker, Viola von Bohlen und Halbach, Oliver von Bohlen und Halbach, Andreas Kuß University Medicine Greifswald, Greifswald, Germany. Nowadays the only bona-fide susceptibility gene for fMNG is DICER1. Introduction: This paper explores the impact of phytochemical compounds found in various amounts in pomegranate, grape seeds and garlic extracts on the levels of gene expression of inflammatory cytokines (IL1b, IL6, IL10) and the variation of this reaction to the genotypes of polymorphism of these cytokines and the relation of this effect to concentration of free radicals. There were no associations in homozygote women or in heterozygotes. Mandel: None. Mustak5, Jordana T. Nishida: B. Given that cfDNA fragmentation is non-random and fragment lengths tend to be overall shorter in cancer, the cfDNA fragmentation state may differ uneven across the genome in healthy and cancer individuals. Birth weight was 3,200 g (75-90th), length 43 cm (18. Acknowledgements: This study was supported by the Instituto de Salud Carlos III [PI12/00879], co-financed by Fondo Europeo de Desarrollo Regional (FEDER) "una manera de hacer Europa", AGAUR from the Autonomous Catalan Government [2017 SGR1134] and Fundación Alicia Koplowitz (AKOPLOWITZ18_001). P12.096.D Multigene panel testing for hereditary breast and ovarian cancer syndrome: experience from a tertiary referral hospital Miriam Potrony 1,2, Blai Morales-Romero1, Lorena Moreno3, Belen Pastor4, Jose L. Currently, we are evaluating the molecular mechanisms by which HYD increases OCT4 and NANOG expression. Iribarren: None. Conclusions: Our results show that ID and skeletal disorders have a unique genetic architecture compared to other disorders. Fantasia: None. WES result: COMP: heterozygous likely pathogenic missense variant c.1293C>A, p.Asp431Glu. MicroRNAs (miRNAs) are small non-coding RNAs observed in biological fluids, where can be shuttled in exosome, extracellular vesicles that play an important role in cell-to-cell communication. Shapland: None. Tkach: None. Right arm and left leg lymphedema became obvious by the age of 5. This enables incident response, root cause analysis, and correction of issues causing contamination. The left eye presented high myopia and retinal pigment deposits. Phenotypic evaluation by physical examination and/or medical records review. Exome sequencing (ES) has revolutionized diagnostic procedures in medical genetics. Sridhar: None. P09.056.A Topological mapping of variant-intolerant domains in SCN1A using a novel functional modeling platform Matteo Vatta, Dianalee McKnight, Karen Ouyang, Ana Morales, Swaroop Aradhya Invitae, San Francisco, CA, USA. Methods: From March 2017 to March 2020, a comprehensive diagnostic work-up including WES was performed in a single academic center in 61 unrelated, critically ill neonates and infants below 1 year of age with an unknown underlying disease. Patient2(P2), boy aged 6 months, was evaluated due to global developmental delay accompanying microphthalmia, cataracts, VSD. Bertrand: None. Carvajal: A. control, time points). van der Helm: None. It is also necessary to single out the procedure of cross-border exchange for the full functioning of biobanks, ensuring autonomous, unified, from the point of view of international rules, legal regulation.The study was carried out with the financial support of the Russian Federal Property Fund in the framework of the scientific project no. Inversions were called using GRIDSS. A retrospective analysis of 13994 de-identified patients that ordered OneOme's RightMed Test during 2019-2020 was conducted in order to identify HLA-B risk allele frequency. We found also a pathogenic deep intronic variant in NF1 gene c.4110+945A>G. Rare arterial complications have been reported, but venous insufficiency is rarely described. Djordjevic: None. P17.009.D Need for speed in whole-genome sequencing data analysis: Benchmarking the new generation of alignment and variant calling tools Sylvan M. No significant differences were observed between different methods of conception (p = 1) with paternal age affecting all methods equally. Metz: None. The EARGEN consortium was initiated to systematically discover new loci underlying HL and conducted the largest meta-GWAS to date. The reasons for extended counseling included medical disorders of the woman or spouse (21.2%), carrier state for autosomal recessive diseases (18.6%), genetic conditions of a child or previous pregnancy (9.6%), or medical disorders in the extended family (79.1%). Zuber: None. Corteville: None. Introduction: ATP8A2 is a member of the P4-ATPase subfamily of P-type ATPases that actively flips phosphatidylserine and phosphatidylethanolamine across membranes to generate and maintain transmembrane phospholipid asymmetry. C.E.J. Sloots: None. We used MR-Radial to identify and exclude such variants from analyses, strengthening the evidence for an association with ER+ breast cancer (OR = 1.04, from p = 4 × 10-9 to p = 3 × 10-16). Hufnagel, Tiffany Powell-Wiley, Beth A. Department of Automation and Applied Informatics Politehnica University, Timisoara, Romania. The aim of this study was to molecularly diagnose 120 Greek patients with different forms of IRDs. Materials and Methods: 120 unrelated Greek patients were analyzed by Next Generation Sequencing (NGS), 13 and 107 of them using a 105 retinal and a 287 ophthalmic gene panel, respectively as described (Ellingford JM et al. Conclusions: a high frequency of mutation carriers is revealed in the Yakut population, which is important both for family planning, as well as for the provision of medical and genetic assistance and the expansion of molecular genetic screening among the population of the Republic of Sakha (Yakutia). Gorduza: None. Six patients were homozygous for a recurrent nonsense variant (c.805C>T; p.(Arg269Ter)); all these patients were of Pakistani origin. P07.021.A Epidemiological of Nosocomial Infection and antimicrobial resistance pattern among different groups of bacteria isolated from some hospitals Jeddah, KSA Molook Al-Ghamdi 1, Effat Al-Judaibi1, Mohammed Al-Rashede2, Awatif Al-Judaibi1 1university of jeddah, Jeddah, Saudi Arabia, 2Maternity and Children Hospital Almosadya, Jeddah, Saudi Arabia. We collected 97 genome-grade DNA samples from consented individuals representing major regions of Ukraine that were consented for the public data release. García-Vallés: None. Funding: The work was funded by the Russian Science Foundation grant number 19-15-00115. Stancheva: None. U.B. Jensen: None. Iemwimangsa: None. P25.003.B Emergency ethical and legal framework for genomic research during COVID-19 outbreak. A.M. Glechyan: None. A third abnormal methylation cluster is suspected to comprise samples with a low tumor cell content due to lower variant allele frequencies of genetic variants and the lack of copy number variants. The ataxia described in the CAPOS syndrome is attributed to cerebellar damage but the implication of a vestibular deficit was present in 2/3 of the patients tested.We have identified the ATP1A3 p.(Glu818Lys) variant in patients with isolated neuropathy with or without inaugural febrile episodes. Higher percentage of microcephaly in PTPN11 and hypertrophic cardiomyopathy in RAF1. As expected, karyotypes of both parents were normal. We map the identified transcriptional profiles to a circuit-level in order to get a better understanding of the molecular mechanisms involved in the brain response to stress. Ghazali: None. Vasilescu: A. For this purpose, 77 selected index patients, with late-onset ataxia (age of onset >35 years) and a compatible pedigree, were screened for the expansion. We also recruited patients with pathogenic TAB2 variants detected by exome sequencing. Employment (full or part-time); Significant; Genos Glycoscience Research Laboratory. Baratela: A. Aretz: None. We report 3 foetuses with ultrasound characteristics and pathology examination with abnormalities associated with CdLS. The highest frequency was found for rs8192579 and rs8192585 NOTCH4 gene. Mean result reporting time was 6 days. Participants were predominantly female (n = 26) and white (n = 31) Interviews were recorded and transcribed, then analyzed using modified grounded theory. The early published variants in these genes are common in gnomAD v2.1.1: 9/11 variants above the disease prevalence (1.08 in 10,000). Illig: None. Slominsky1, Maria Shadrina1 1Institute of Molecular Genetics of National Research Centre «Kurchatov Institute», Moscow, Russian Federation, 2Pirogov Russian National Research Medical University, Moscow, Russian Federation. They both had hypertrophic cardiomyopathy (HCM), which resolved spontaneously. Harris3, Jacqueline A. Meester: None. Further studies should be performed to clarify the involved mechanism. Single cells were genotyped using cellSNP-lite. Macquère: None. We aim to present the first paper examining the health-related utility of RD using an established QoL measure - the Assessment of Quality of Life-8D (AQoL-8D). Discussion: The use of ddPCR to screen for specific, highly relevant mutations as T315I that confer resistance to treatment holds great promise. Relative BC risk reduction (RRM versus non-RRM) was 94%. Schlegelberger: None. Kalinkin2, Ekaterina B. P11.114.D Genetic testing algorithms for fetal malformations malformations Viorica Radoi 1, Radu-Ioan Ursu1, Cristina Dragomir2, Andreea Ionescu2, Iuliana Chelu2, Laurentiu Camil Bohiltea1 1INSMC Alessandrescu-Rusescu, Bucharest, Romania, 2Synevo Romania, Bucharest, Romania. Lyangasova: None. Lopez: None. Patients from 6 families were found to have a distinct type of Pontocerebellar Hypoplasia with typical basal ganglia or thalami involvement on neuroimaging. To the best of our knowledge the ERCC2: c.1867dup variant has not been previously reported in the literature and is a frame shift-type variant. Boerwinkle: None. Haplotype analyses showed a significant association with HbA2 for the two di-nucleotide haplotypes combining the minor alleles rs3817621/rs79334031 CA (beta = 0.591; p = 0.036) and rs79334031/rs2072597 AC (beta = 0.921; p = 0.020), and a near-significant association for haplotype CAC (beta = 0.614; p = 0.075). A GSS haplotype rs1801310G-rs6088660C-rs13041792A (OR 1.26, 95CI 1.08-1.47, Pglobal = 0.039) showed a significant association with T2D risk. V.A. Michailova: None. M.C. Braunisch: None. There are plausible genetic mechanisms causing the cardiac and anal anomalies seen in our patient and suggest the PACS2 disease spectrum should be expanded. Conclusion: The analysis of the largest Russian cohort of AKU patients allowed us to established the peculiar mutational spectrum, characterized by significant prevalence of c.481G>A; p.(Gly161Arg) mutation. Introduction: Pompe disease is caused by the accumulation of glycogen in the lysosome due to deficiency of the lysosomal acid alpha-glucosidase (GAA) enzyme. Only changes associated with the patient's phenotype below 500 kb were re-analysed. A.E. Karamova: None. Tavares: None. Madrigal: None. At molecular-level miR-29b inhibition caused alteration on miRNA pattern (11 downregulated and 8 overexpressed) assessed using microarray technology on BT549. Gruber: None. Cabrera de León: None. Materials and Methods: DNA methylation patterns in the promoter or regulatory regions of 4 genes (GCLM, GSTP1, TXNRD1, and MPO) in peripheral blood leukocytes of 45 patients with CAD and in 83 sex- and age-matched healthy controls were analysed. Bone marrow aspiration revealed a hemophagocytosis. We were able to identify all gene variants expected from the panel at high allele frequency. Introduction: TAB2 loss-of-function variants and deletions including TAB2 are associated with congenital heart defects and cardiomyopathy. Continued investigation of COVID-19 in rare disease backgrounds will inform diagnosis-specific health guidance. Hayhurst: None. The cold pressor test (CPT) is used as pain provocation test in pain research. Le nabec: None. Paternal haplogroups U5a and K increased the risk of developing ASD in offspring. Filtering germline exome data according to the overrepresented pathways, found in each subgroup, and also tumor signatures did not identify recurrent rare variation within the different groups. Jaklič: None. Tumours located in hypopharynx and larynx were linked with break in CSMD1 gene. Materials and Methods: We have developed an approach based on a modification of anchored multiplex PCR followed by NGS for deep multiplex fragment lengths profiling that simultaneously targets 25 tumor-specific open-chromatin regions in cfDNA. Pinasa: None. Morbidoni: None. Bakhshalizadeh: None. Compliance with treatment is complicated by the remote location. P17.038.A Plasma: a versatile e-learning platform for teaching interactively genomic and genetic data analysis with Jupyter notebooks Claire Vandiedonck 1, Pierre Poulain2, Sandrine Caburet2 1Université de Paris, INSERM, Centre de Recherche des Cordeliers, F-75006 Paris, France, 2Université de Paris, CNRS UMR 7592, Institut Jacques Monod, F-75013 Paris, France. HHT is caused by pathogenetic variants in ENG, ACVRL1, SMAD4 and GDF2, belonging to the TGFβ/BMPs pathway. Additionally, we investigated students' intolerance of uncertainty, and self-reported anxiety when hypothetical parents indicated to consider termination of pregnancy (TOP) based on the result. The patient's clinically unaffected father was mosaic for this change (VAF of 30%). Conclusion: Both of our patients with NTHL1 deficiency and adenomatous polyposis had various extracolonic disease manifestations, including breast cancer. The gene-set analyses found associations with HOXB7 and HOXB3. Results: WES revealed a de novo variant in TRAF2 and a deletion which encompasses 52 genes, including KDR. Discussion: Previous reports proposed candidate genes for DD/ID within 6q11q4 region, namely KCNQ5, which is deleted in our patient. The prevalence of this mutation was: 2.9% in suspected HPP group (15/518), 0.28% (2/706 chromosome) in home controls, 0.25% in gnomAD. Consultant/Advisory Board; Modest; Novartis, Sanofi Genzyme, Almirall, TEVA, Merck-Serono. CNV analysis included a proprietary method for exon-level CNVs. Variant interpretation followed ACMG guidelines. Fourteen families have completed testing to date. Our genetic and functional data in mouse and zebrafish implicate SHROOM4 in the expression of a human VATER/VACTERL phenotype. Pieri: None. Y chromosome includes genes for testicular development and spermatogenesis. We selected instances where at least one repeat was found in an exon or when both repeats were flanking an exon. Results: Analysis of the FTD pool data led to the prioritization of 9 pathways with a total of 18 genes associated with plasma lipoprotein assembly, remodeling, and clearance. Gaslini, genova, Italy. Conclusion: BRD4-related phenotype is part of the CdLS spectrum but is characterized by clinically relevant specificities that distinguish it from other cohesinopathies. A definitive diagnosis of PD allows proper patient management and more precise genetic counselling of patients and families. Stambouli: None. Introduction: Autosomal dominant polycystic Kidney Disease (ADPKD) though rare, is the most common hereditary kidney disease. P12.097.A Unravelling genetic predisposition to familial breast and ovarian cancer: identification of new susceptibility genes by case-control study Alejandro Moles-Fernández 1, Ester Aguado-Flor1, Cristina Zamarreño1, María Antolín2, Sandra Bonache1, Adrià López-Fernández1, Lídia Feliubadaló3,4, José Fernández-Navarro1, Conxi Lázaro3,4, Judith Balmaña1, Orland Díez1,2, Sara Gutiérrez-Enríquez1 1Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, 2Vall d'Hebron University Hospital, Barcelona, Spain, 3Catalan Institute of Oncology (ICO), Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), Hospitalet de Llobregat, Barcelona, Spain, 4Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain. Libraries from the liquid handler system required 5Gb more to achieve the same. Nemr: None. de Boer: None. Importantly, EM measurements displayed a 43% reduction of lesions and a significant decline of the lesions-severity in the GBM of 4-PBA treated mice. Methods: We evaluated a consanguineous family with three-years-old male living child and five abortions. This PRS was also associated with longer survival in an independent sample of younger individuals, (p = 0.02), leading up to a 4-year difference in survival based on common genetic factors only. Introduction: Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by synovial inflammation and destruction of cartilage and bone. Materials and Methods: Nine SRNS patients, initially screened for NPHS1, NPHS2 and WT1 mutations, were recruited. The other variants were novel. Botia: None. Sanger sequencing confirmed the mosaicism for the mutation. P12.012.D Frequency of pathogenic variants in BRCA1 and BRCA2 genes in a Russian population-based sample and in patients with breast or ovarian cancer Alena Limonova 1, Alexey Meshkov1, Alexandra Ershova1, Anna Kiseleva1, Olga Skirko1, Marina Klimushina1, Evgeniia Sotnikova1, Olga Kurilova1, Irina Efimova1, Ludmila Lyubchenko2, Margarita Filippova2, Andrey Poloznikov3, Vladimir Kutsenko1, Maria Pokrovskaya1, Oxana Drapkina1 1National Medical Research Centre for Therapy & Preventive Medicine, Moscow, Russian Federation, 2N.N. Blokhin National Medical Research Center of Oncology, Moscow, Russian Federation, 3National Medical Research Radiological Center, Moscow, Russian Federation. Results: DDL is a cellular and typically non-lipogenic sarcoma with significant pleomorphism. Ioseliani: None. P10.022.B Somatic mosaicism for Duchenne muscular dystrophy in an asymptomatic 4 year-old boyAna-Maria Meašić1, Ivona Sansović1, Adriana Bobinec1, Leona Morožin Pohovski2, Mijana Kero1, Ljubica Odak 1, Ingeborg Barišić1 1Department of Medical Genetics and Reproductive Health, Children's Hospital Zagreb, Scientific Centre of Excellence for Reproductive and Regenerative Medicine (CERRM), University of Zagreb School of Medicine, ZAGREB, Croatia, 2Department of Medical Genetics and Reproductive Health, Children's Hospital Zagreb, University of Zagreb School of Medicine, ZAGREB, Croatia. Cocca: None. Conclusions: FluiDMD RNA profile accurately addresses the gene region where atypical mutations may have occurred and WGS accurately identified the two inversions. Introduction: Hypertension, insulin resistance, abdominal obesity, decreased HDL, and high triglycerides co-occur as the metabolic syndrome at substantial health cost. Our findings expand the genotype-phenotype correlation of DC; thus underline the importance of integrating clinical information, molecular data and TL to facilitate the recognition of the etiopathogenesis of telomere syndromes. Yet, the susceptibility genes with different strengths of evidence are scattered in literature without professional data integration and comprehensive analyses. Suveges: None. Lang-Andrey: None. Results: We analyzed 132 DNA samples (n = 32 families). We aimed to evaluate the association of the p.R577X with sports injuries in Slovenian female football players. The highlight of the results was decrease in the freqeuncy for total number of common disorder cases (50,2% to 42,4%). It is important to alert clinicians to the possibility of detecting this syndrome for a correct treatment during infancy and surveillance during adult age. According to the MCC analyze of CytoHubba there were 10 hub genes with rank = 1 for Russians (CUL1, ANAPC11, LNX1, CDC20, UBE2L6, FBXO9, KLHL13, UBA3, KCTD7, RNF111) and Yakut (KLHL3, FB11PSXL, ASB2, LRRC41, LMO7, RNF7, SKP2, FBXO2). Our observations do not rule this out completely, but strongly stress the importance of genetically encoded CNV in DMBT1 protein variation. Conclusions: For cases in which the fusion cannot be detected from the peripheral blood, bone marrow analysing should be considered, given the fact that patients with FIP1L1-PDGFRA fusion benefit from imatinib treatment. Conclusions: This case expands the clinical spectrum of primary COQ10 deficiency-6 and underscores the importance of screening for multiple system disease, including cardiac evaluation, in these patients. Introduction: The aim of the study is to find out how experts look at the growth of popularity of genetics, how they describe the expectations and requests from the government and society, what problems, in their opinion, they face in the development of scientific knowledge in Russia. Statistical analysis was performed using Fisher's exact test. The most frequent were mutations in genes: GJB2 - 16 cases, DHCR7 - 11, PAH - 9, NEB - 7, AIRE - 6, ATP7B - 6, C9 - 6, DUOX2 - 6, HADHA - 6, MPO - 6, CFTR - 5, GALT - 5, IDUA - 5, PKHD1 - 5. The NSGC has prioritized the development and promotion of PROMS for assessment of service value and to support reimbursement for clinical services. Methods: APC-specific adaptations of the interpretation guidelines published by the American College of Medical Genetics and the Association of Molecular Pathology (ACMG/AMP) were suggested based on expert opinions, database analyses, and literature search conducted by the VCEP. We compared ONS to molecular karyotyping for the detection of pathogenic CNVs to demonstrate its clinical utility. P20.050.A Tanycytes and Co. A single cell analysis of the brain third ventricle Maxime Brunner 1, Federico Santoni1, Fanny Langlet2 1CHUV, Lausanne, Switzerland, 2University of Lausanne, Lausanne, Switzerland. Dragicevic: None. Clinicians can benefit from our tool to make an informed decision on which accessible tissue is most suitable for RNA-seq and increase the diagnostic chances. X-linked genes were analysed differentiating males and females: in females, MAGEA2, MAGEA3, MAGEA4, UXT and FLNA displayed the highest methylation levels in non recurrent PitNETS, lower levels in recurrent PitNETS and no methylation in carcinoma. Materials and Methods: Adult PHTS patients who visited our expertise centre between 1997-2020 were included (N = 87). Afroze: None. Pesevska, V. We accompany the results with a rich web-resource allowing the user to explore in detail similar genes based on a query gene. Sequencing results were analyzed using the Ion Reporter Software. Elliott: None. Supported by RFBR (project № 19-015-00122 A), within the state task of the Ministry of education and science of Russia V.V. Kadyshev: None. Giovanni di Dio Fatebenefratelli, Brescia, Italy, 4Department of Medicine, Surgery and Health Sciences, University of Trieste, Trieste, Italy. Results: In the remaining twelve cases, pulmonary valve stenosis was found in seven cases; atrial septal defect was identified in 3 cases, aortic coarctation, aortic regurgitation and hypertrophic cardiomyopathy were each identified in two cases, pulmonary regurgitation, heart failure, aortic dysplasia, ventricular septal defect and coronary sinus dilatation were each identified in one case. Introduction: Epilepsy is a multifactorial and heterogeneous disorder that occurs mainly due to structural, metabolic, immunological and genetic reasons. Gouya: None. Ownership Interest (stock, stock options, patent or other intellectual property); Significant; PolyKnomics. Boucher Brischoux: None. Thus, the translation of disease-associated non-coding variants into a functional model is challenging and further limited by the availability of cellular models and the presumed time point- and tissue specific effect of the variants. 390(32%) of the 1221 postnatal consultations used tele-technologies. P07.027.C Biological miR-146a-TRAF6 axis is associated with lupus flares and renal fibrosis progression Olga Martinez-Arroyo 1, Ana Ortega1, Javier Perez-Hernandez2, Ana Flores1, Josep Redon3, Maria J. Here, we report a 14-year-old male patient who was admitted to our clinic with seizures, developmental delay history, and mild intellectual disability. Plaisancie: None. Introduction: Interstitial deletions of the long arm of chromosome 2 involving the 2q32q33 region encompass SATB2 gene. Pérez-Alonso: None. a: retinal vasculopathy, nephropathy, anaemia, Raynaud's phenomenon, liver disease, migraine, stroke, and vascular dementia b: hypertension, muscle cramp, dry mouth, migraine, stroke, and vascular dementia c: hair loss, degenerative spine disease, backpain, anaemia, migraine, stroke, and vascular dementia d: cataracts, anterior segment dysgenesis, kidney cyst, haematuria, muscle cramp, myalgia, arrhythmia, Raynaud's phenomenon, haemolytic anaemia, migraine, stroke, and vascular dementia e: stroke and vascular dementia A.C. Ferguson: None. Duboys de Labarre: None. Hodel: None. Quélin: None. Poeta: None. Parents and older sibling are healthy and heterozygous for one or another mutant allele. Hypotonia, intellectual impairment, stereotypic demeanor, brain structural anomalies and strabismus compose their phenotype. Conclusions: Alteration in the composition of SMAD4 transcripts can be attributed to change in levels of transcripts other than SMAD4-201 and SMAD4-202. Associated craniofacial malformations include cleft palate, choanal atresia, zygomatic arch cleft and facial asymmetry. Traeger-synodinos: None. Sánchez-Monteagudo: None. Our study expands the phenotypic spectrum of CIII Core protein deficiency, provides insight into the assembly pathway of human CIII, and supports the requirement of assembled CIII for a proper accumulation of CI. de Knijff: None. The STAP1:NM_012108.3:c.526C>T:p.(Pro176Ser), was conserved and in silico predictors showed damage. These included rs35011184 (TCF7L2) and rs2981578 (FGFR2), previously reported for many of five studied outcomes. Materials and Methods: Parents were notified of the study through social media and were requested to upload a microarray report. These results highlight the importance of unbiased genetic analyses in clinical settings. After a comprehensive filtering process, two variants of SLC25A42 were confirmed with Sanger sequencing and fully segregated in the tested family members. Minelli: None. Targeted validation in blood and urine supported pathogenicity, with heteroplasmy levels of 23% and 58% in index, and 4% and 17% in mother, respectively. Turchetti: None. Additionally, we utilised the exome data of 5,784 genetically proven fathers. 448/603 (74.3%) patients had cleft palate, 132/603 (21.9%) had cleft lip +/- palate and 23/603 (3.8%) had oral clefting. The SBayesR prediction models that included on average 1,090,196 genetic polymorphisms explained up to 21% of glycan variance (36% of SNP-based heritability). Michaud: None. Alvarez-Mora: None. Here, we investigated LEF1 isoforms expression and genomic variations in acute lymphoblastic leukemia (ALL). Changes in alternative promoter activity might lead to alternations in expression pattern of transcripts with alternative 5' ends, making them potential cancer biomarkers. Jacquin: None. Wallace2, Sacha J. Dijkhuizen: None. Catarino: None. This tool contributes to seeking a diagnosis, to improve the early treatment of NDD and to support the family during a diagnosis of a rare and severe disease. Results: 145 of all 2414 detected proteins showed differential abundance (FDR G/p.(Ala39Gly) + + + + + - + + Missense Benign SRD5A2 c.265C>G/ p.(Leu89Val) - - - - - + - - Missense Benign SRD5A2 c.226T>A/ p.(Ser76Thr) - - - - - + - - Missense Not reported SRD5A2 c.89dupC/ p.(Pro31Ser31fsTer225) + + + + + + + + Frameshift Benign AR c.2257C>T/p.(Arg753Ter) - - + - - - - - Nonsense Pathogenic AR c.2323C>T/p.(Arg775Cys) - - - - - + - - Missense Pathogenic AR c.404C>T/ p.(Pro135Leu) - - - - - + - - Missense Uncertain Significance AR c.170T>A/ p.(Leu57Gln) - - - - + - - - Missense Likely benign AR c.1368_1379del/p.(Gly470_Gly473del) - - + - - - - - In-frame Deletion Uncertain Significance +: Presence, - : Absence P. Mounier: None. Differentially expressed genes could be identified during hierarchical clustering of the LG group against HG_MIBC. Patients, and Results: Case 1, 3-years-old boy with developmental delay, hypothroidism, iridocorneal dysgenesis, glaucoma, midface hypoplasia, thin upper lip and enamel hypoplasia on incisor teeth. Results: The 18-SNP PRS was significantly associated with an increased breast cancer risk in Cypriot women. We performed WES in 3,319 consecutive samples (2016 through 2020), referred for genetic testing in a wide variety of diseases. Chantot-Bastaraud: None. Thereby, we detected known recurrent fusion events in 26 cases that were not reported by routine. Each mixed TCR/BCR repertoire was obtained by multiplex PCR with subsequent Illumina sequencing and data analysis using MiXCR software. Katz: None. The liquid biopsy also detected the same mutations with mutation rates 0.44% and 0.38%, respectively. Cano: None. The interviews were analyzed using an inductive thematic approach. Moka: None. Tomiak: None. 2014;35(11):1271-1279). Heterozygotes 23525TA of the FTO gene predominated (45%) among boys with normal sexual development. P09.121.B Developing expression system for evaluation of SCN1A splicing alterations Peter Sparber, Kseniya Davidenko, Margarita Sharova, Alexandra Filatova, Mikhail Skoblov Research Centre for Medical Genetics, Moscow, Russian Federation. Notably, for MSC and ATF3, this finding was supported by a strong quantitative effect on the predicted binding change, which for MSC is currently validated using in vitro assays. A.M. Duca: None. Vaher: None. His brother had aortic dilatation and aortic insufficiency. Since PTC bearing transcripts are subject to degradation by nonsense mediated decay, we hypothesize that an increase in gene expression by a histone deacetylase (HDAC) inhibitor in combination with triamterene will lead to a greater increase in enzyme activity than triamtrene alone. Susgun: None. Pathogenesis is governed by defects in many genes involved in multiple developmental pathways. Genetic information includes family health history as well as data resulting from the analysis of biological samples. Pearson: None. We hypothesized such effects will be confirmed in the placenta. Ahmed: None. Materials and Methods: Clinical reports of 543 patients who underwent panel testing at Blueprint Genetics with an indication of suspected skeletal dysplasia or growth disorder were examined. S.A. Ahmed: None. We showed that the timing of RRS remains suboptimal, especially in women undergoing RRSO. tevko: A. Methods: A multidisciplinary working group was formed in late 2019 under the auspices of the BSGM ethics and policy committee to update the 2010 BSHG genetic testing of children guidance. Quental: None. Gebauer: None. A significant association between the genotypes regarding ANO7 gene's SNP and metastasis to the axial skeleton was detected (p = 0.024). P02.030.C A RIPOR2 in frame deletion is a frequent and highly penetrant cause of adult onset hearing loss Jeroen J. Results were consistent in sensitivity analyses. Materials and Methods: We retrospectively collected clinical and genetic data of 22 probands and 74 family members. The significant pathway scores were then tested, using PheWAS, against disease traits in UK Biobank. s., Brno, Czech Republic, 2Unilabs Slovensko, s. DNA methylation profiling microarray analysis was performed on the proband's tumor sample, providing a profile that was consistent with the signature characterizing embryonic rhabdomyosarcomas. R.A. Illarionov: None. Introduction: Next-generation sequencing technologies have facilitated the sequencing of genomes of human and non-human organisms, leading to an immense amount of variant data. This situation gave us the idea of a possible presence of gonadal mosaicism in the mother. Coustier: None. PGT is practiced worldwide, allowing to prevent transmission of a growing number of genetic conditions. After shearing, we placed the samples and kit reagents on the liquid handler, in their original reagent vials. In the present study, we sought to identify significantly altered miRNAs and genes involved in DCM by integrating left ventricular myocardial genome-wide microRNA and mRNA expression profiling and explore the mechanisms underlying the disease. Although germline alterations in candidate genes e.g. SRGAP1, SRRM2, FOXE1; have been identified in FNMTC, these have been in isolated individuals or single/paired families. Casas Alba: None. Conclusions: Collectively, we strongly suggest that GAPDH will be the most suitable and stable reference gene and protein for the CCD1079Sk. The RPLP0 gene was found unstable during each passage and using the RPLP0 gene as a reference may be misleading. In addition, we provide enrichment analyses based on neighbouring genes establishing whether genes close to each other are also enriched for biological processes or UK Biobank disease traits. Results: Using the panel MovDisord-498, 20 patients achieved a genetic diagnosis. Recommendations included relate to: Accelerating the use of new tools in preventing hereditary breast cancer, the use of these tools in breast cancer prevention pathways, and moving towards risk-stratified population screening. STAR software and DESeq2 package were used for mapping and defining differentially expressed genes. Groups further divided by paternal age, young (45 years of age at conception). Garcia-Pelaez*: None. A.A.L. Jorge: None. Rescenko: None. Multi-locus imprinting disturbance (MLID) is defined as multiple imprinting defects across the genome and has been described in miscarriages, recurrent hydatidiform moles and in some congenital imprinting disorders (CIDs). Idéfix therefore is not yet able to identify every sample mix-up. Twenty patients (80%) had facial features suggestive for Noonan syndrome. Várhegyi: None. Sex modifies both disease risk and heritability, with higher incidence in males and higher rates of mother to daughter transmission. References:1- Greifenberg, A. Miro PCR-free WGS libraries (n = 178) were prepared using sheared gDNA inputs (75-500ng) from multiple sources (NA12878 and donor blood samples). Parman: None. Each PKD1 variant was identified in a single family, and one family had 2 linked variants. Dueñas: None. P04.079.D IRAK2 is associated with rheumatoid arthritis susceptibility Rim Sghiri 1, Hana BenHassine2, Asma Boumiza2, Khadija Baccouche3, Foued Slama2, Adel Almogren1, Zahid Shakoor1, Elyes Bouajina3, Ramzi Zemni2 1King Saud University, Riyadh, Saudi Arabia, 2Faculte de Medecine de Sousse, Sousse, Tunisia, 3Hopital Farhat Hached de Sousse, Sousse, Tunisia. Malignant arrhythmias in CAS and SCD victims are mainly due to pathogenic variants in genes associated with ACM, LQT2, CPVT and LQT3. He obtained head control at 7 months. Grants: SFI 17/CDA/4737 R.P. Byrne: None. Current detection methods rely on PCR- or hybridization-based techniques that do not allow the detection of novel fusion breakpoints. There is increasing evidence of transposable element (TEs) activation during tumorigenesis. It has to be mentioned that along with EGFR-Ex19del a patient has also a high PD-L1 overexpression (>80%). In three families, affected siblings were discordant for the molecular findings. Data was split by embryonic day to yield a developmental time frame. Patient's mtDNAcn variation between tumor and adjacent-normal tissue was expressed as ratio, and cohort subdivided into two groups according to the median. Dideberg: None. Mikhalov: None. Drapkina1 1National Medical Research Centre for Therapy and Preventive Medicine, Moscow, Russian Federation, 2Bauman Moscow State Technical University, Moscow, Russian Federation. Caporali: None. Partial genetic correlation between CWP and depressive symptoms, body mass index, age of first birth, and years of schooling were identified. We set up a 21-amplicon targeted sequencing workflow for analyzing mutations in the EGFR pathway. D'Abrusco: None. This research was funded by Colciencias contract FP44842-122-2016. UMAP was computed on a publicly available computer infrastructure. SHS is characterized by variable degrees of intellectual disability with language skills typically affected, hypotonia, epilepsy, behaviour issues, feeding difficulties, constipation, cryptorchidism, short stature, and structural malformations (cardiac, brain, ocular, kidney and skull anomalies). Freidin: None. Nambot: F. Materials and methods: The male patient with choroideremia, deafness and intellectual disability underwent the whole-exome sequencing (WES). Bujanda: None. G.Y. El-Kamah: None. Consultant/Advisory Board; Modest; Janssen, Bayer, Astellas Pharma, Sanofi, Orion Pharma, Curevac, Astra Zeneca, ESSA Pharma, Roche, Amgen. Abstract: SCRIB gene is a member of planar cell polarity (PCP) genes which are involved in the process of neural tube closure (1).Homozygous Scrib mutations in mice cause craniorachischisis, the most severe typeof NTD. We systematically measured and classified the diverse patterns of clustered mutations in tumors focusing on APOBEC activity. D.S. Westphal: None. Additionally, in 11 cases, variants in interesting candidate genes were found which should be further explored for functional validation. Conclusions: The progressive symptoms allowed to suspect and genetic testing confirmed the diagnosis of A-T. Duffin: None. In collaboration with medical geneticists and oncologists, the molecular laboratory of Karaiskakio Foundation (KF), offers whole exome sequencing (ISO15980 accredited since 2019) using SureSelect Human All Exon V7 (Agilent CA, USA) to patients with hereditary cancer or rare syndrome suspicion that were otherwise molecularly undiagnosed. These disorders include brain growth abnormalities such as microcephaly (MIC), megalencephaly (MEG), and malformations of cortical development (MCD; such as lissencephaly, polymicrogyria). Sanger sequencing was used to verify NGS results and determine the segregation of the presumably pathogenic variants in available first degree relatives. The c.35delG variant accounts for 38.1% (16/42) in Ossetian patients with GJB2-associated HL and 12.3% (16/130) in the total sample. Kaya: None. P06.024.A Functional characterization of 3'UTR LDLR variants in Familial Hypercholesterolemia Javier Sanguino 1,2, Carmen Rodríguez-Jiménez1,3, Jose María Mostaza4, Elena Sevilla1,2, Amanda Herranz-Cecilia1,2, Ana Carazo1,2, Olga Pernía5,6, Carlos Rodríguez-Antolín5,6, Inmaculada Ibáñez5,6, Sonia Rodríguez-Nóvoa1,2 1Metabolic Disease Laboratory, Genetic Department. Further studies will explore the impact of additional AF loci on risk stratification and determine if PRSs can be integrated into clinical practice. Testing for the (AAGGG)n expansion in genetically undiagnosed patients with late-onset ataxia (particularly those with the typical clinical triad) is highly recommended. Their interpretation using different databases found twelve candidate genes and three candidate pathways, including Hippo-YAP/TAZ pathways. Conclusion: We plan to study the role of candidate modifier(s)/pathways in dystrophic zebrafish and identify novel mechanisms to attenuate LAMA2-RD severity. In order to further delineate the ARID2 phenotypic spectrum, we report a cohort of twelve unrelated individuals harboring ARID2 deletion or pathogenic variants and we compare their features with those previously described. Sethi: None. The recent discovery of the new genome editing biotechnology called CRISPR-Cas9 has raised huge debates in this revision process. Armengol Dulcet: A. Trgovec-Greif: None. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Modest; ISGlobal. All these findings occurs as a result of accumulation of hyaline-like material in the skin and mucosa. There was little evidence of effect modification on the other eight cardiovascular traits or of sex-specific effects. P16.014.A Validations of genotyping array analysis as a diagnostic method in medical genetics Martina Witsch-Baumgartner 1, Silja Burkhard1, Beatrix Mühlegger1, Rebekka Gröbner1, Gunda Schwaninger1, Peter Kirchmeier2, Johannes Zschocke1 1Medical University Innsbruck, Innsbruck, Austria, 2JSI medical systems GmbH, Ettenheim, Germany. Results: a novel MYO6 intragenic deletion was identified in the proband. Lopera-Maya 1, Alexander Kurilshikov1, Adriaan van der Graaf1, Shixian Hu1, Sergio Andreu-Sánchez1, Lianmin Chen1, Arnau Vich-Vila1, Ranko Gacesa1, Trishla Sinha1, Valerie Collij1, Marjolein A. These variants included whole-gene deletions, gene duplication, gene fusions, recombinant exons, and phased compound heterozygotes. However, clinical findings are heterogeneous in relation of size, material in p or q arm and mosaicism/nonmosaic. Jezkova: None. PCR-free WGS protocols were compared to manual and high-throughput liquid handler library preparation: 1) Miro PCR-free WGS Library Prep Kit with mechanical fragmentation, 2) Illumina DNA PCR-free Prep Kit with tagmentation. Corton: None. Farra: A. Introduction: Whole exome sequencing (WES) is often the most efficient and most widely available diagnostic tool for patients under investigation for a Mendelian disorder, however, a significant proportion of clinical exomes (60%-75%) is non-diagnostic. Introduction: Neurodevelopmental diseases affect 2%-3% of the general population, and have highly clinical and genetic heterogeneity, which complicates the genetic diagnosis. Hernandez Paredes: None. Conclusion: WES is a powerful non-invasive diagnostic tool in critically ill neonates and infants with a high diagnostic rate. K.U. Ludwig: None. The work was supported by RFBR grant #19-015-00331 G. Conclusions: We provided no support for causal relationships between VVs of lower extremities and knee OA. She was a carrier of a homozygous PV in NTHL1, c.268C>T p.(Gln90*). Intelligence in the normal range is a polygenic trait, and there are influenced at least 500 genes. Conclusion: While this finding will allow the selection of the appropriate management of the future pregnancies, it invites to further discussion about when to proceed to WES in cases of normal CMA with long ROHs, regardless ultrasound results. The siblings are compound heterozygous for c.283G>C(Ala95Pro) and c.523G>A(Gly175Arg), which are likely pathogenic variants according to the scientific databases. RNAseq showed complex splicing events for c.1029+2T>C and c.151G>C. Early detection, as well as rapid, well selected treatment, are key factors leading to good prognosis. Grote: None. Coenen6, Mirian Janssen7, Dylan Henssen8, Christian Gilissen9, Wouter Steyaert9, Ida Paramonov3, Solve-RD-DITF-ITHACA, Aurélien Trimouille10, Tjitske Kleefstra1, Alain Verloes11, Lisenka E. Osei: None. Brady: None. CLN2 is a severe, rapidly-progressive neurodegenerative disease with seizure onset at or after 2 years of age. Salumets: None. Of all nonNCCN-HBOC FA genes FANCM, FANCD2 and FANCA were most frequently mutated. Results: scMuffin provides functions to calculate a series of qualitative and quantitative scores, such as: expression of markers for normal and tumor conditions, pathway activity, cell hierarchy, multipotency state, copy number variations and cell cycle state. He evolved with arterial hypertension, and severe mitral regurgitation with MVP diagnosed at 30 years, requiring mitral valve plasty and anticoagulation therapy for two years. We studied two groups of Tibetans, one from high altitude (4500 meters above sea level (masl)); another migrated to low altitude (~880 masl) about ~60 years ago. TTD1 hiPSC-bKs showed reduced expression of FLG and SPRR2B in line with previous reports and mouse models. Lohmann: None. Mazzeo: None. The impact of reproductive risk factors on BC was also evaluated. Aretz*: None. S.F. Nelson: None. Urvantseva: None. Affected patients present with intellectual disability and other comorbidities. After QC, we found 2 differentially methylated probes (pvalue adj ≤ 0.1) in CACNA1G, expressed mostly in brain, and VAX1 genes; while filtering by delta beta (Δβ) values, we identified 2 probes with Δβ ≤ - 0.25 (in an intergenic region and RUSC1-AS1) and 2 probes with Δβ ≥ 0.25 (in AARS and KPNA4). Introduction: Genome editing techniques, in particular, CRISPR-Cas9, could correct a wide range of gene mutations. Age at diagnosis of first tumor was 36-76 years. Especially through more than 100k genomic copy number number (CNV) profiles from over 500 cancer types, Progenetix empowers comparative analyses vastly exceeding individual studies and diagnostic concepts. P19.056.D Evaluating the causal role of serum phosphate on bone mineral density: a Mendelian randomization study Haotian Tang, Jie Zheng, Tom R. One of them is the known CRC predisposing gene CHEK2. Results: This method revealed the E255K/V and T315I mutations in the BCR-ABL gene in two samples. We observed an increase of TEs being causal for gene expression changes in tumor compared to normal (Fisher P = 6.34e-11) and identified 79 triplets where TEs become causal for changes in gene expression for 51 cancer driver genes (5 CRC-specific) in tumor making these TEs potential drivers of cancer driver genes. Willemsen1, Lisenka E. G.D. Carrasquilla: None. Methods: We performed RNA-sequencing on RNA obtained from muscle samples of the atypical patient, the affected sibling and unrelated LAMA2-RD patients with both total and partial merosin deficiency. Conclusion: The CDC20-rs710251 and PLK2-rs15009 could potentially be useful for survival prediction. Translation may greatly widen the website's readership, especially for individuals with genetic conditions, their relatives and the general public. Individuals were divided by quartiles of metabolite concentrations into case and control groups according to: total cholesterol (6.81 - case, mmol/l), triglycerides (1.77), HDL-cholesterol (>1.65, 1.81, G (p.Tyr386Cys) predicted to be deleterious. Nguyen: None. Results: 274 genetic variants located on 205 genes were prioritized. Methods: Whole exome sequencing (WES) was carried out in a proband with PAH and primary biliary cirrhosis. To date, the trio analysis of WES is powerful in detecting qualitative DNA changes, but nearly blind in recognizing small quantitative changes like intragenic deletions/duplications. A.V. Tikhonov: None. Case report: A 3-month-old girl, who was diagnosed with severe bilateral hydronephrosis at 15 weeks of gestation, presented post-natally with cleft palate, bilateral volar nails of the fifth finger and second toe and lacrimal duct obstruction. Ambrozaityte: None. It provides a view for the expansion of gene spectrum associated with thoracic aortic aneurysms and dissections, which will be helpful for the clinical diagnosis and clinical intervention. J.L. Lühmann: None. The consequences of the variations were in silico analyzed, and the possible effects were discussed at the protein level. Discussion/Conclusion: CF is associated with liver involvement around 30%. Dubowsky: None. Results: 9 cases collected (3 females/6 males). Aytac Vuruskan: None. Mirault: None. Berard: None. Spasova: None. P04.078.C The HRAS-RIN1 signaling axis controls integrin trafficking in keratinocytes and its dysregulation contributes to the epidermal manifestation in Costello Syndrome Theresa Nauth, Laura Isabel Brandenstein, Verena Rickassel, Georg Rosenberger University Medical Center Hamburg-Eppendorf, Institute of Human Genetics, Hamburg, Germany. The effect of the mutation on protein is predicted as damaging by in silico analysis. van Bokhoven1,2, E-J. J.A. Martinez-Agosto: None. Mellibovsky: None. Conclusion: Our findings suggest that loss of CYHR1 causes autosomal recessive neurodevelopmental delay. Several of NCCN-HBOC genes belong to Fanconi anemia (FA) pathway. Results: MLPA revealed a change in exon 10 of DMD. Moreover, we also used 3D culture to assess the exosomes uptake and to observe their capability of internalization into a 3D structure. Introduction: Ribosomopathies caused by abnormalities of ribosomal proteins and on biogenesis factors are a broad spectrum that affects various tissues including the nervous system, bone marrow, and ectoderm or causes developmental-delay or cancer-susceptibility. Vecchio: None. EEG showed a discontinuous pattern with interemispheric asymmetry and a cortical electrogenesis disorder in the absence of epileptiform abnormalities. Conclusion: The PRS predicts CHD in both men and women and impacts age at CHD onset. Clinical data of the patient were collected from the medical record. This work was supported by RSF grant №20-75-10091 and RFBR grant №20-015-00462. Caburet: None. The RASopathies are one of the largest known groups of malformation syndromes and affect approximately 1:1000 individuals worldwide. Two variants in ATM and FANCM are novel. P11.133.C A ZFHX4 mutation associated with a recognizable neuropsychological and facial phenotypePaolo Fontana1, Monia Ginevrino2,3, Kristel Bejo2, Giuseppina Cantalupo1, Maria Ciavarella1, Cinzia Lombardi1, Marianna Maioli1, Francesca Scarano1, Antonio Novelli2, Fortunato Lonardo 1 1AORN San Pio, Benevento, Italy, 2Bambino Gesù Children's Hospital, Roma, Italy, 3Università Cattolica del Sacro Cuore, Roma, Italy. SureCall application (Agilent) was used for end-to-end data analysis. Hagleitner1, Hans Gelderblom2, Anne-Marie Cleton-Jansen2, Judith

V. Here we report a patient with an atypical DASS phenotype. P06.043.D Mitochondrial DNA mutations do not impact early human embryonic development Kalliopi Chatzovoulou 1, Anne Mayeur2, Nadine Gigarel1, Fabienne Jabot-Hanin1, Laetitia Hesters2, Arnold Munnich1, Nelly Frydman2, Jean-Paul Bonnefont1, Julie Steffann1 1Imagine Institute, Paris, France, 2Antoine Beclere Hospital, Clamart, France. Heterozygous mutations in the MME gene cause autosomal dominant spinocerebellar ataxia-43 (SCA43), which is a slowly progressive neurologic disorder characterized by adult-onset gait, limb ataxia, and often associated with peripheral neuropathy. Results: Phenotypic analysis of reported individuals reveals novel PIGG deficiency associated features. Capri: None. Connaughton: None. Ludwig1 1Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Bonn, Germany, Bonn, Germany, 2Institute of Human Genetics, University of Heidelberg, Heidelberg, Germany, Heidelberg, Germany. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Modest; Roche, Astra Zeneca, Biocartis, Illumina. The exomes of 60 HSAN patients and, if available, unaffected family members were sequenced. The proteins and exact mechanism behind these movements remain not understood. Doherty, Laura O'Briain, Jennifer Hengeveld, Éanna MacDomhnaill, Orla Hardiman, Russell L. Anastasovska: None. In familial hypercholesterolaemia, 101/262 individuals were mutation-positive by sequencing; mutation identification by array was achieved in 68/262 individuals (26%). J.M. Wilmshurst: None. P13.036.A Dissecting expansion dynamics and nucleotide variation in human-specific variable number tandem repeatsMeredith M. Results: Three variants previously reported were found in heterozygous in three patients in STAP1 two of them with frequency G (p.Thr17Ala) is reported in ClinVar as pathogenic. Material and Methods: A Tunisian 29-years-old female was referred to us for brachial plexopathy. Certain CFTR variants are defined as "CF" alleles causing CF phenotype, and other alleles are defined as "risk factor" alleles, causing CBAVD, pancreatitis and atypical CF. Here we describe a case of SRS-MLID associated with maternal variants in MEGs.Methylation profiling of 63 genomic regions containing imprinted DMRs was undertaken in a female child diagnosed with SRS and compared to healthy controls. To overcome these limitations AWMGS has developed a web application for analysing WGS cases. This disorder is caused by germline mutations in the tumor suppressor gene STK11, located on 19p13.3, encodes for the LKB1 protein comprising 433 amino acids and belonging to the serine/threonine kinase family. Thus, an ultrasound anomaly led to the serendipitous discovery of the second pathogenic mutation, which otherwise would have been missed according to prenatal checks. At 11 loci, candidate genes had established relationships with cardiomyopathies in humans, including MYH7 and TNNT2. Alenius: None. Main phenotypic outcome was age at onset (AAO) of the symptomatic disease and a Kaplan-Meier analysis of disease symptom event-free survival was performed. C.J. Bult: None. To evaluate telomere length and its effect on OR values in healthy women with a diagnosis of PCOS. Lermine: None. Case report: We report about an 18 month old girl with global developmental delay, muscular hypotonia, microcephaly and mild facial dysmorphisms. Conclusions: Patients with a small, unrepaired ASD were enriched for rare PAVs within 59 ASD candidate disease genes. Acknowledgement: This research was supported by the Science Fund of the Republic of Serbia, PROMIS, #6052315, SENSOGENE. This is a 65-year-old female, which underwent last year a right upper lobectomy being diagnosed with micropapillary and acinary adenocarcinoma. HiFi reads were generated from libraries and consensus amplicons were produced using pbAA. S.M. Maas: None. Conclusion: We describe the third family with multiple malformations in three conceptuses with identification of the biallelic variant c.365_367del; (p.Thr122del) in exon 5 of HHAT in the living proband. Ercan Sencicek: None. Method: Liquid biopsy via circulating tumor DNA (ctDNA) in blood test results were collected from a 62-year old patient with stage IV (T3N0M1) colorectal cancer after one month, three months and one year of surgery. In the subset of individuals tested through BTS who were aged 24-60 months with seizure onset at or after 24 months (n = 3,263), the molecular diagnostic yield was 7.9% overall (n = 259) and 0.61% for TPP1 (n = 20). E.Y. Bragina: None. Segregation analysis in the family showed de novo origin. Kebir: None. Lottaz: None. Introduction: The aim of this study is to investigate potentially curable or treatable medical conditions in unselected newborns using genomic sequencing (GS). hiPSCs were successfully differentiated into basal keratinocytes (hiPSC-bKs), with high expression of epidermal keratins 5 and 14. In our MP-GWAS, these yielded the best model fit for T2D- and breast cancer-only, respectively. We showed that unsupervised methods were not able to discriminate time points, while supervised clustering did significantly distinguish time points using metabolomics and/or transcriptomic data, but not using conventional clinical measurements. CCD exhibit genetic and clinical heterogeneity with diverse underlying pathomechanisms. Perkins3,2,4, Juan A. Real-time PCR showed that mRNA expression of the mutant PTRHD1 is higher compared to wild-type. From these results, PheWAS identified numerous associations between these pathways and traits in UK Biobank such as lymphocyte and leukocyte count but also height, weight and lung-function traits. Two nucleotide variants in MYO5B gene were detected. The main group consisted of 370 obese children and adolescents and 150 non-obese children and adolescents (control). Scherbak, Y. Methods: Targeted NGS analysis (custom panel HIPOPIT_V3; 310 genes) of three generations family members (n = 12). S.E. de Bruijn: None. Nascimento-Filho, Vilson Serafim-Junior, Márcia M. Predesigned oxidative stress 96-well plates were used to perform qRT-PCR analysis. The analysis was focused on BRCA1, BRCA2, ATM, CHEK2, BRIP1, BARD1, PALB2, ATM, and TP53 genes. Spaander1, Anja Wagner1, Maartje Nielsen2 1Erasmus MC, Rotterdam, Netherlands, 2Leiden University Medical Center, Leiden, Netherlands, 3Netherlands Cancer Institute, Amsterdam, Netherlands. IIS - University Hospital Fundación Jiménez Díaz, Universidad Autónoma de Madrid (IIS-FJD-UAM), Madrid, Spain, 5Department of Pathology. Strikingly, one missense variant affects an amino acid that was previously involved in GD. The 49 genes shared by the three annotation terms suggest a possible interesting novel ferroptosis-seizure relationship (Fisher´s Exact for the overlap P = 5.95x10-12). In this manuscript we present a family with a previous clinical diagnosis of Tel Hashomer camptodactyly syndrome. In this study, we propose a novel method for analyzing multiple omics in a single, multivariate analysis, using the flexibility and computational power of neural networks. The analysis of male baldness phenotype in UK Biobank exome data showed a strong association with the Androgen Receptor (AR), a gene that was also found to be associated with the phenotype by GWAS. Saverimuttu: None. Pelc: None. In physical examination, eunuchoid body, sparse axillary and pubic hair growth, small testes, bilateral gynecomastia, digital ulcers, telangiectasias, and splenomegaly were detected. Physicians from specialities particularly involved in the management of these patients (clinical geneticists, paediatric endocrinologists, paediatric cardiologists) were invited via SurveyMonkey, with support from several European societies. Dinur: None. Introduction: Despite (neo)adjuvant chemotherapy with cisplatin, doxorubicin and methotrexate in primary osteosarcoma, some patients progress during first-line systemic treatment and have a poor prognosis. One of the explanations is that cells with derivative chromosomes divide rarely in cell cultures, leading to conclusion that aCGH is more accurate technique for detecting mosaic chromosomal imbalances. One of them arised from precursor adenomatous polyp. D.R. Shaw: None. Introduction: Among the PGT-M cases with a history of affected children homozygous for a recessive mutation, transfer decision of heterozygous embryos becomes challenging in case where the mutation is associated with an additional disease with autosomal dominant inheritance. Clark: None. Selicorni: None. UPDs are relatively rare (Nakka et al. Results: This study identified new associations between: cholesterol levels and rs940806 (p = 0.00718), rs4947995 (p = 0.03076), rs12536061 (p = 0.03076), rs1111650 (p = 0.03076), rs10774519 (p = 0.04462); hypertonia and rs878847 (p = 0.0263). Travessa: None. Highton: None. Conclusions: Our study focuses on undescribed features in SS, expanding the clinical and molecular spectrum and advising clinicians about some unreported clinical complications. Rarer mutations, such as the W1282X and the c.711+1G>A variants, were detected in 1 patient each. The majority of ALS cases are sporadic, while 10% are familial. According to the BMI they are divided into four groups – underweight (n = 2), normal weight (n = 2), overweight (n = 2), and obesity (n = 2). Tissue and cell enrichment analyses underlined the role of the urogenital system and muscle smooth cells (p 2-5 cm; lymph node, oestrogen receptor, progesterone receptor and HER2 status: positive/ negative; tumour differentiation grade: G1+G2/G3) and SNPs was evaluated using χ^2 test. Marlin: None. Human papilloma virus (HPV) is the etiologic agent of cervical cancer and the third most commonly diagnosed type of cancer in women worldwide. Thus, the detection of novel KMT2A chimeras in pediatric AML is important to improve the treatment stratification and disease monitoring. Pagella: None. In all countries, training included Clinical and Laboratory practice, although the proportions of these components varied widely. The obtained genomic data was then surveyed for the presence of PRR variants and their frequency in the two pools was calculated. We suspect that parental mosaicism might be more common than previously thought for P4HB variants. The fetus suffered intrauterine demise at 30 weeks gestation. Materials and Methods: We automated several steps of the ACMG scoring scheme, proposing clinicians the recommended choices along with enclosed explanatory genomic annotations. Employment (full or part-time); Significant; Medigenome, Swiss Institute of Genomic Medicine. Poirsier: None. It usually presents in toddler years with progressive ataxia and oculomotor apraxia, or less commonly, in the late-first or early-second decade of life with mixed movement disorders. Lindee: None. Bollet: F. An electronic search of the literature revealed just 25 cases of EC diagnosed during or after pregnancy, for the period between 1995 and 2019. M.I. Schouten: None. P12.164.D Yield of thyroid cancer surveillance in patients with PTEN Hamartoma Tumour Syndrome Meggie M. We also analysed the association between the exosomal miR-146a and TNF receptor associated factor 6 (TRAF6 axis). Additional recommendations and statements were formulated (Wagner et al. Schmalz: None. Methods: We used data from 52,254 participants in UK-Biobank without a previous diagnosis of cardiovascular disease. Pagliazzi: None. Kralska: None. Interestingly, presence of MEGF10 associated EMARDD has not been reported in the Saudi Arabia, a highly consanguineous population. Malhorta: A. Hollox University of Leicester, Leicester, United Kingdom. P11.036.B A functional mutation in HDAC8 gene as novel diagnostic marker for cornelia delange syndrome Xueren Gao Shanghai Institute for Pediatric Research, Shanghai, China. Iskandar: None. C.E.M. de Die: None. A.V. Lavrov: None. Cunningham: A. After this, we performed analysis for runs of homozygosity shared between brother and sister, and found a single 2,3 Mb homozygous block on chromosome 11q24.1 which contained 46 homozygous variants in 19 genes, of which only 1 was likely pathogenic: a previously not described frameshift mutation in exon 3 of the ESAM gene (NM_138961.3; c.287delC/ p.Pro96fs). R.V. Veiko: None. Two exhibit patellar subluxations. We invited these laboratories to complete a questionnaire to rate their satisfaction with each report component, overall length and layout. Maslennikov: None. Through the numerous associated phenotypes, GDF5 illustrates the difficulties in interpreting genomic variations. A subset of PIDs is caused by pathogenic germline variants in DNA repair genes. 24 previously published intronic variants and one novel missense variant were then testes for splicing alteration. Saetta: None. These findings allowed us to refine the template, producing a tool which will assist laboratories to improve their reporting practices. NGS identified mosaic nonsense mutation c.[986=/C>A] in exon 10 of DMD with 70% of reads containing alternative allele A. This classification is based on the expression of protein coding genes, messenger RNAs (mRNAs). 166(7.5 %) by video and the rest by telephone. Introduction: Hereditary angioedema (HAE) is a rare disease caused by C1 inhibitor (C1-INH) deficiency or dysfunction or dysregulation of the kinin cascade (HAE-nC1-INH). Monasky: None. Hassib: None. Search for a variants in noncanonical and canonical exons 6 was performed by Sanger sequencing. L.V. Gutnikov: None. Georgiou: None. Ergun: None. ZOEMBA is a Dutch multicenter study of our UMD consortium that aims to establish a diagnosis in 500 IMD patients via integrated multi-omics analysis. This analysis revealed overall similarities between the patients with two noteworthy clusters of similar facial gestalts: one with two individuals (missense variant and small deletion) and one cluster with six individuals including our patients (frameshift, nonsense, and small deletion variants). Szyszkowski: None. N.E. Caporaso: None. Introduction: Marfan syndrome (MFS) is the best known congenital disease of connecting tissue. Conclusions: This study for the first time ever demonstrated an association between a genetic variant of TRAF6 and low BMD among patients with RA. 2509962099. Montaño: None. Döttelmayer: None. Mean diagnostic delay was 1.71 ± 1.53 years (significantly longer in type IV patients). We have sought to evaluate the utility of incorporating CCRs into the diagnostic filtering cascade of RD patients that have undergone genomic sequencing and, specifically, determined the contribution Dns play in improving diagnostic rate. Sanger sequencing revealed de novo pathogenic variant c.830C>A in exon 8 in the PTEN gene in patient D. Introduction: There are more than 200 heritable connective tissue disorders. Complete genetic characterization of these events was unreliable by WGS because the breakpoints lie within SDs. Consequently, we used Bionano optical mapping to fully characterize these chromosomal abnormalities. Eikenboom 1, Anne-Sophie S. Plaza: None. Ten years after NIPT has been made commercially available, it is increasingly entering routine antenatal care as either a first- or second-tier test. The main goal of our study was to evaluate the changes in the frequency of these anomalies in the Czech Republic and the overall effectiveness of their prenatal diagnostics. Abadie: None. All patients and their families were evaluated by a craniofacial clinical geneticist. Whereas de novo occurrence strongly supports pathogenicity of a variant in commonly used diagnostic pipelines for next generation sequencing, inheritance from a seemingly healthy parent generally downgrades it. Conclusions: Whole-genome sequencing of nearly healthy individuals could be useful in the early prevention of cancer development and in offspring planning. After received adjuvant postoperative treatment with 5-FU in April 2018, intensive follow-up for CEA19-9 and CEA were 6.18 ng/ml and 2.18 U/ml, respectively. Parodi: None. Boehm: None. Table 1. Romero Blanco: None. Lambrechts: F. This suggests that decisions on when to test the germline in persons with MLH1 promotor hypermethylation and a BRAF V600E mutation need to be carefully considered. Sanger sequencing confirmed that he had deleterious hemizygous X chromosome variant in PQBP1 (NM_001167989:p.Arg153fs) inherited from an unaffected heterozygous mother. P01.029.A Assisted reproductive technology can be a risk for epimutation-mediated imprinting disorders for mothers over 30 years Kaori Hara-Isono 1, Keiko Matsubara1, Masashi Mikami2, Takahiro Arima3, Tsutomu Ogata4, Maki Fukami1, Masayo Kagami1 1National Research Institute for Child Health and Development, Tokyo, Japan, 2National Center for Child Health and Development, Tokyo, Japan, 3Tohoku University Graduate School of Medicine, Sendai, Japan, 4Hamamatsu University School of Medicine, Hamamatsu, Japan. Steinke-Lange: None. P15.023.C GRIN2B novel de-novo variants the cause of patients with generalized severe hypotonia as primary referral conditionFAIDON NIKOLAOS TILEMIS1,2, NIKOLAOS M. Zechi-Ceide1, Nancy M. Analysis identified the cause of the disease in 49 patients (49%). Palover: None. Estiar1,2, Prabhjyot Saini1,2, Konstantin Senkevich1,2, Yuri L. Some MRI showed not specific alterations. T.R. Gaunt: None. Differences between specialties and countries were statistically assessed. Methods: We used results from the largest genome-wide association studies of European ancestry for accelerometer-based physical activity and sedentary time in up to 91,105 individuals, and for BMI in up to 694,649 individuals. for patients with mutations in residue 756 - Fever-Induced Paroxysmal Weakness and Encephalopathy (FIPWE), next Sabouraud et al. Vázquez-Mojena: None. Gene ontology (GO), canonical pathways analysis (IPA), gene set enrichment analysis (GSEA) and weighted gene co-expression network analysis (WGCNA) to identify co-expressed modules and hub genes were used to explore the biological functions of the dysregulated genes. Introduction: X-chromosome inactivation (XCI) occurs randomly; however, skewing can occur in 3.2-3.5% of females. Michalovská: None. These pathways are primarily immune response pathways, such as NOD-like receptor signalling and Toll-like receptor signalling. Results: In this study, we identified STXBP1 mutation p.Arg192Trp that have not been reported previously and was homozygous, what is rather unusual in the case of this gene. The CSRI-Ra was developed. DNA-methylation profiles were obtained by using the Illumina Infinium Methylation 450K Beadchip. Results and discussion: Spanish is the first language of approximately 480 million people worldwide, predominantly in Mexico (122 million), Colombia (49.4 million), Argentina (44.1 million) and Spain (42.9 million). Our aim was to evaluate the concordance between Next-generation sequencing (NGS) and Sanger Sequencing for mutation detection in exon 9 and 20 of PIK3CA gene. Hamel: None. Employment (full or part-time); Significant; Geneton Ltd. D. M.C.W. Spaander: None. P19.012.D Natural selection analysis for GWAS SNPs in cytokine genes Maryam B. Yield was lower in families with premature birth compared to birth at term. Lorenzo-Diaz: None. Linear regressions between genotypes and methylation levels were performed using TensorQTL in a ±1 Mb window, adjusted by sex and five principal components. Muzio: None. The enrichment of known cholesterol lowering targets among the top hits demonstrates the robustness of our approach while also suggesting some alternative genes for follow-up. Keane: None. For instance, when selecting the 10% of participants for whom predicted phenotypes adhere best to the actually measured phenotypes, we estimate that the proportion of sample mix-ups is reduced 250-fold. Mehta, Kenneth Olivier, D. Non-invasive prenatal diagnosis (NIPD) for SCD is desired by patients, but complicated by the high background of the maternal mutation and frequent unavailability of paternal samples. Compound heterozygous or homozygous missense and frameshift variants in the FARS2 gene, that encodes the mitochondrial phenylalanyl-tRNA synthetase, are commonly linked to either early-onset epileptic mitochondrial encephalopathy or spastic paraplegia. The family members were heterozygous carriers of the same variant detected in the index case. This allowed identification of respiratory problems in KdVS not reported previously, and of differences in behavioural manifestations between the 3 syndromes. Understanding this heterogeneity could provide valuable insights for prognostic markers. Rendulic: None. Results: MLPA detected six abnormalities (9.7%): two deletion 22q11.21, two unbalanced translocations (dup 3p/del 7q; del 4p/dup 11p) and two terminal deletions (del 18p; del18q). Zampino31, A. Also a significant positive correlation was between del32/allele genotypes of CCR5 gene in patients and duration of stay on oxygen therapy using an oxygen mask (r = 0.455, p = 0.044), stay on lung mechanical ventilation (r = 0.760, p = 0.047) and the total duration of oxygen therapy (r = 0.467, p = 0.029). Kadyshev, Nika V. Variants were classified according to ACMG guidelines. P08.084.B WES result reanalysis and CAMK2B variant causing developmental delay Todor Arsov 1,2, Aspazija Sofijanova3, Marcin Adamski2, Carola Vinuesa2 1Ss. Cyril and Methodius University in Skopje, Faculty of Medicine-Skopje, Institute of Immunobiology and Human Genetics, Skopje, Macedonia, The Former Yugoslav Republic of, 2Australian National University, John Curtin School of Medical Research, Centre for Personalized Immunology, Canberra, Australia, 3Ss. Cyril and Methodius University in Skopje, Faculty of Medicine-Skopje, PHI University Clinic for child diseases, Skopje, Macedonia, The Former Yugoslav Republic of. Filip: None. González: A. In order to define the placenta methylome compared to cord blood by means of an ontology- driven approach, we explored the LINE-1 methylation profile in cord blood and placenta samples from 154 uncomplicated full-term pregnancies, and the genome-wide methylation pattern by methylation array (Infinium EPIC array) in ten pregnancies and by targeted methylation sequencing (Methyl-Seq) in other five pregnancies. Gene ontology analysis of these DMRs showed enrichment (>2.0-fold change) of genes associated with regulatory pathways involved in nervous system development and differentiation. Magi: None. The analysis determined that the developing pancreatic diseases are more common from the age of 40 (P = 6x10-5). Henderson15, Timothy Blake Palculict15, Sureni V. Introduction: MERRF is a mitochondrial encephalomyopathy caused by mtDNA mutations in the MT-TK gene, always found heteroplasmic with a high threshold for the expression of the pathologic phenotype. DiNonno: A. It has been observed that rare variants tend to be less pleiotropic than common ones, which suggests that highly pleiotropic variants with large effect sizes are subjected to strong purifying selection. Introduction: Autosomal recessive osteopetrosis (ARO) is a rare genetic disorder of bone resorption caused by defective osteoclasts resulting in increased bone density. On X-rays of limbs club-shaped enlargement of the metaphysis of the distal femur and the proximal tibia were described. Gonzalez Granero: None. Introduction: Glycosylphosphatidylinositol (GPI)-anchored proteins are glycolipids found on many blood cells and served to anchor other proteins to the cell surface. Experimental replicates and calculation of loss-of-function scores using other DNA damaging agents is ongoing. Follow-up with cytogenetics karyotyping at 21 weeks of gestation was performed, which revealed a result of apparently normal male karyotype 46, XY in cultured amniocytes. APOGeE will connect with other online knowledge sources. High arched feet and brisk reflexes at the knees were reported. Paperna: None. Patients were recruited as active co-researchers who reported their thoughts, feelings and family discussions about the "life world" within which their decisions are made. Four variants of uncertain clinical significance were detected in tumor DNA by using the CCP and the IonChef/S5 platform; known cancer driver mutations were not detected. P08.034.D DDX3X syndrome phenotype heterogeneity a case report and literature review Rossella Colantuono 1, Maria Chiara Rocco1, Dario Di Salvio2, Maria Tessitore1, Lucia Nazzaro3, Domenico Viggiano1, Maria Teresa Falco3, Giorgia Mancano4, Tjitske Kleefstra5, Lot Snijders Blok5, Matteo Della Monica6, Pietro Vajro1, Daniela Melis1 1Pediatrics, Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, Baronissi (SA), Italy, 2Pediatrics, University of Naples "Federico II", Napoli, Italy, 3"San Giovanni di Dio e Ruggi d'Aragona" University Hospital, Salerno, Italy, 4Meyer University Hospital, Firenze, Italy, 5Department of Human Genetics, Radboud University Medical Center, Nijmegen, Netherlands, 6Department of Medical and Laboratory Genetics, Cardarelli Hospital, Naples, Italy. Churkin: None. Lundstam: None. López González: None. Results: The metabolic syndrome traits were more correlated than traits in general (P = 3.9E-6). Hachmeryan: None. D.G. Calame: None. The altered bioavailability of integrins in keratinocytes expressing HRASGly12Ser was associated with impaired cell spreading. Funding: This work was supported by Novo Nordic Foundation (Grant no. This work is supported by the Russian Foundation for Basic Research [grant number 20-515-12009]. T.V. Nikitina: None. Introduction: De novo GRINB2 mutations are found in a wide range of neurodevelopmental disorders resulting in epileptic encephalopathy and mental retardation with/without epilepsy. Pagnamenta6, Reza Maroofian7, Christian Beetz8, Hermine van Duyvenvoorde9, Maria Lisa Dentici1, Peter Lauffer10, Sadeq Vallian11, Andrea Ciolfi1, Simone Pizzi1, Peter Bauer8, Nana-Maria Grüning8, Emanuele Bellacchio1, Andrea Del Fattore1, Stefania Petrini12, Ranad Shaheen13,14, Dov Tiosano15,16, Rana Halloun15, Ben Pode-Shakked17,18, Hatice Mutlu Albayrak19, Emregül Işık20, Jan M. Among them pathogenic variants in KCNQ1, KCNJ2, SCN5A, RYR2 genes were identified. Whetzel: None. P11.006.D Clinical findings in 22q11.2 microdeletion syndrome: case series Sule Altıner, Timur Tuncalı, Nüket Yürür Kutlay, Halil G. SHOX-deficiency causes a spectrum of clinical phenotypes related to skeletal dysplasia and short stature including Léri Weill dyschondrosteosis, Langer mesomelic dysplasia, Turner syndrome, as well as idiopathic short and tall stature. Eight genes are associated with autosomal recessive osteopetrosis. P08.043.A GenIDA, an international participatory database to get an insight into the natural history and co-morbidities of genetic forms of neurodevelopmental disorders Jean-Louis Mandel 1,2, Pauline Burger1,2, Axelle Strehle1,2, Florent Colin1,2, Timothée Mazzucotelli1, Nicole Collot1, Amélie Piton1,2,3, Pierre Parrend2,4, Laurence Faivre5,6, David Geneviève7, Valentin Ruault7, Thomas Smol8, Roseline Caumes9, Joost Kummeling10, Charlotte Ockeloen10, Tjitske Kleefstra10, David Koolen10 1IGBMC, Illkirch, France, 2Université de Strasbourg, Strasbourg, France, 3Unité de Génétique Moléculaire, Hôpitaux Universitaires de Strasbourg, Strasbourg, France, 4ECAM Strasbourg-Europe, Schiltigheim, France, 5Equipe Génétique des Anomalies du Développement, Université de Bourgogne-Franche Comté, Dijon, France, 6Centre de Génétique et Centre de Référence Anomalies du Développement et Syndromes Malformatifs, FHU TRANSLAD, Hôpital d'Enfants, CHU Dijon et Université de Bourgogne, Dijon, France, 7Université de Montpellier, Centre Hospitalier Universitaire Montpellier, CLAD Sud Languedoc-Roussillon, INSERM, Montpellier, France, 8CHU Lille, Institut de Génétique Médicale, RADEME, Lille, France, 9CHU Lille, Clinique de Génétique Guy Fontaine, Lille, France, 10Department of Human Genetics, Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Center, Nijmegen, Netherlands. Results: A signature of 29 dysregulated circulating miRNAs was identified in UAE hypertensive subjects, regulating 21 pathways. Rendu: None. McLaughlin1 1Smurfit Institute of Genetics, Trinity College Dublin, Dublin, Ireland, 2Academic Unit of Neurology, Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin, Ireland. Macek Sr.: None. Conclusions: By investigating face profile variations in an admixed population, we were able to identify new regions associated with human face traits. Carrasco: A. Putative enhancers were prioritized for follow-up studies by overlapping cerebellar/SH-SY5Y 4C-seq data with publicly available SH-SY5Y/cerebellar ATAC-seq, ChiP-seq and Dnase-seq data. Consultant/Advisory Board; Modest; Medday, Biogen Idec, Merck-Serono, Excemed, Roche, Sanofi Genzyme, Teva Pharmaceutical Industries. The patient's karyotype confirmed premature centromere separation (PCS)/heterochromatin repulsion (HR). MLH1 epimutations can appear secondary to a genetic alteration in cis and following an autosomal dominant pattern of inheritance (secondary epimutations), or as a de novo event associated with null or non-mendelian inheritance (primary epimutations). Wilson5,13, Arthur Gilly1, Eleftheria Zeggini1,2 1Institute of Translational Genomics, Helmholtz Zentrum Munich, Neuherberg, Germany, 2TUM School of Medicine, Technical University of Munich and Klinikum Rechts der Isar, Munich, Germany, 3Centre for Global Health Research, Usher Institute, University of Edinburgh, Western General Hospital, Edinburgh, United Kingdom, 4MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, United Kingdom, 5Centre for Global Health Research, Usher Institute, University of Edinburgh, Edinburgh, United Kingdom, 6Biostatistics Group, State Key Laboratory of Biocontrol, School of Life Sciences, Sun Yat-sen University, Guangzhou, China, 7Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, 8Anogia Medical Centre, Anogia, Greece, 9Echinos Medical Centre, Echinos, Greece, 10Department of Nutrition and Dietetics, School of Health Science and Education, Harokopio University of Athens, Athens, Greece, 11Department of Medicine, Karolinska Institutet, Solna, Sweden, 12Emerging Science & Innovation, Pfizer Worldwide Research, Development and Medical, Cambrige, MA, USA, 13MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Western General Hospital, Edinburgh, United Kingdom. Alves Grilo Gonçalves: None. Chwiałkowska: None. Škerl: None. Early diagnosis of IMDs is key as many are amenable to treatment. Finally, these data, for the first time, evidence that HYD regulates OCT4 and NANOG expression in human somatic cells. Less is known about the effect of assisted reproduction techniques (ART) on the number of DNMs in offspring. Inversions, i.e. a change in orientation of a segment of DNA, are a recognized cause of human diseases. Holowatyj6,7, Juan L. Liskova: None. Materials and Methods: 84 Crohn's disease patients naïve to adalimumab treatment were enrolled in the present study. In order to elucidate the genetic background of FVH, we performed WES in eight trios recruited at Meyer Children's Hospital in Florence. Height and weight were under 3th percentile. Prenatal WES analyses enabled us to provide pertinent genetic counseling and to offer targeted prenatal diagnosis in case of a new pregnancy in 35.8 % of our couples. Gregersen Aarhus University Hospital, Aarhus N, Denmark. Al Hashmi8, L. Kaler1,2,6, Maria M. The results were obtained within the RSF grant № 17-15-01051. Asparaginyl-tRNA synthetase1 (NARS1) belongs to the class IIa family, based upon a 7 beta-strand protein structure, and functions in the cytoplasm responsible for asparagine tRNA charging in these locations. Nardecchia: None. The library was prepared using Agilent Sureselect VI exome Kit and analyzed with a NovaSeq sequencing platform. Conclusion: Our patient harbours a hemizygous Xq21 deletion of a smaller size than similar CNVs reported in the medical literature thus far. As TECPR2 has no published crystal structure, we established a pipeline to predict 3D protein models based on three different algorithms (GalaxyTBM, swissmodel, trRosetta). Epidemiological studies show sociodemographic-mediated differences in outcomes, but less is known about case incidence and severity in rare disease populations. The genetic analysis was performed by whole-exome sequencing. Results: Table 1 displays the distribution of in criteria (IC) vs. Arnaud: None. Helbig: None. According to previous GWAS involving 1980 samples from the Western European populations of Spaniards and Italians, a severe course of COVID-19 (respiratory failure) was associated with rs11385942 and rs657152 (Ellinghaus et al., 2020). P25.004.C Role of the FYVE and Coiled Coil Domain Autophagy Adaptor 1 in severity of COVID19 infection Sandra P. Sundqvist23, M. The patients were contacted prior to their appointments to determine their preferences for appointment type before being taken through the pre-symptomatic testing process. Results: we identified a homozygous frameshift variant c.396dupT (p.Val133CysfsTer18) in 4th exon of CLN6 gene in all patients. Vallespín: None. Giunti: None. 0.038, P = 2e-4) and total span of long-sized ROHs (186 vs. Individuals were eligible for testing through BTS if they were aged 24-60 months with unprovoked seizure onset at/after 24 months (Dec 2016-Feb 2019) or, following program expansion, aged 0-60 months (Feb 2019-Jan 2020) or 0-108 months (Jan-Nov 2020) with unprovoked seizures onset at any age. The machine-learning strategy predicted psychosis with an area-under-the-curve of 66 % (non-parametric p = 0.009), and 207 Δmirna were confidently leveraged for prediction, with bootstrapped 95% confidence intervals excluding zero. As genome-wide association studies (GWAS) have identified disease specific associations, so too has the possibility of bioinformatically exploring the comorbidity and causality between risk-factors and diseases and the influence of genetics. Ballard: None. Kitsiou - Tzeli: None. Acknowledgements: This work was supported by Grants DH03/14/19.12.2016/NSF; D01-285/17.12.2019,MES, Bulgaria. Syndromological, "Face2gene", cytogenetic, molecular genetic, instrumental methods of examination were used. Also, typical dysmorphic features were noted in 75% (21/28) of patients. FISH analysis with a NF2 probe revealed that this gene was rearranged. Dimartino: None. Genovese: None. Marić: None. This method highlight changes that are likely to impact genetic diagnosis predicated on ClinVar submissions processing by interquartile range outlier detection, reclassification monitoring and agglomerative clustering. Smeding: None. M.N.C. Formiga: None. He had lean body build, muscular atrophy of upper back and scoliosis. V.M. Vorontsov: None. Conclusion: Our findings suggest that rare, highly penetrant variants of genes involved in glutamatergic neurotransmission are contributing to etiology of schizophrenia in these families. While the 60% of patients carrying a missense/missense genotype presented symptoms before or at the first year of life, almost all patients with at least 1 truncating allele (91%) had an AAO ≤1 year (Log Rank test p G, p.Gl386Arg was classified as probably pathogenic according to LOV.3 and CLINVAR. arr 8p11.23p11.1 (37,348,105-43,754,516)x3. WES performed in a second patient (P2) showing, as well as P1, intellectual disability, round face, ptosis and strabismus revealed the heterozygous variant c.1447_1450delGTCA (p.Val4834argfsTer11) in BRPF1; cerebral MRI at 1 and 3 years were normal. Results: We found the pathogenic variant c.1486C>T, p.Arg496Cys in the SMAD4 gene, this variant was determined as de novo with the segregation analysis. This panel was validated with at least 25 samples with excellent results. Consultant/Advisory Board; Modest; AstraZeneca, MSD, Tesaro, GSK, Illumina, Myriad Genetics, Roche. Eltaraife3, Amal S. Pinto Leite: None. P20.028.C Characteristics of DNA methylation of the regulatory region of the MLH1 gene in peripheral blood leukocytes of patients with common age-related diseases Nadezhda P. Palomero-Gallagher: None. O.R. Olusanya: None. Wolkenstein: None. H.M. Huang: None. Introduction: MUTYH-associated polyposis (MAP) is an autosomal recessive polyposis syndrome caused by biallelic pathogenic variants (PVs) in MUTYH gene. Keywords: CCD, TNNI3K I. Abe: None. Lewis: A. La Bianca: None. We prepared semi-targeted RNA-seq libraries from prostate cancer cell line RNA and clinical samples and sequenced them. Conclusions: NS provides unbiased whole genome methylation calling and a faithful representation of the CpG profiles in various genomic contexts. Concern has been raised for BLK, KLF11 and PAX4 as causes of MODY - a dominant form of monogenic diabetes. PacBio HiFi sequencing produces long and accurate reads to identify variant regions. Abella: None. Epstein-Barr Virus (EBV) infects >90% of the population. PD is multifactorial, with genetic variation in over 30 genes involved in PD risk, development, onset and progression. For example, pathogenic Dn variants intersecting a CCR were overrepresented in the NND group (p = 8.13x10-06) but underrepresented in the Ophthalmological group (p = 2.47x10-07). P19.021.A association of FTO (rs9939609), LIPC 250 G>A and LPL Ser447Ter gene polymorphisms with obesity in children and adolescents Lyudmila Valerievna Gutnikov 1, Alaa H. The average age of participants is 46 years old, with 50% females. The implementation of NGS allows to test that patient´s biopsy also for variants for which drugs are yet under development, or for rare variants still allowing the patients to benefit from personalized therapy. P12.054.B Contribution of Pathogenic Variants in Genes Predisposing to Colorectal Cancer by Pan-Cancer Panel Testing Frida Eiengård 1,2, Anna Rohlin1,2, Torbjörn Olausson1,2, Ulf Lundstam3, Margareta Nordling1,2 1Department of Laboratory Medicine, Institute of Biomedicine, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden, 2Department of Clinical Genetics and Genomics, Sahlgrenska University Hospital, Gothenburg, Sweden, 3Department of Surgery, Sahlgrenska Academy at University of Gothenburg, Sahlgrenska University Hospital/Östra, Gothenburg, Sweden. Donati: None. The recognition of familial balanced chromosomal rearrangements is crucial for genetic counselling, because if they are inherited the recurrence risk changes radically. Material and methods: 202 autoimmune thyroiditis patients and 340 healthy subjects without previous history of autoimmune disease were recruited. A newborn infant underwent routine NBS in our institute that showed elevated methionine in the first and the recall sample. Introduction: The most common disorders of lipid metabolism are LDL-hypercholesterolemia, HDL-hypocholesterolemia, hypertriglyceridemia. For the analysis of the ATXN1 and ATXN2 genes repeat sizing was used. Due to the specificity of the MMIC knowledge scale, versions are specific to subspecialties and must represent current information. Then, we extracted key terms, mapped them to HPO when possible, and checked them against our repository to test our method. P04.085.B Monogenic variants in short stature: use and efficiency of targeted NGS panel in 300 patients Caroline Michot 1, Pauline Marzin1, Geneviève Baujat1, Coralie Haudry2, Anne-Laure Tourre2, Julie Steffann2, Sophie Rondeau2, Valérie Cormier-Daire1 1Reference Center for skeletal dysplasia, INSERM UMR1163, Paris Descartes-Sorbonne Paris Cité University, Imagine Institute, Necker-Enfants Malades Hospital, Paris, France, 2Molecular Genetic Unit, Paris Descartes-Sorbonne Paris Cité University, Necker-Enfants Malades Hospital, Paris, France. Kuo: None. A.V. Markov: None. Understanding the association of WNT signaling components with spermatogonia proliferation/differentiation; induction of apoptosis in postmitotic germ cells could help elucidating the etiology of azoospermia. Vione: None. The hazard ratios (HRs) (95% confidence interval [CI]) for individuals in the top versus bottom 20% of the distribution were 17.2 (10.7 - 27.7) versus 14.9 (9.3 - 23.7). For the last 15 years there were complaints of persistent cough, exacerbations of chronic bronchitis about 2 times a year. Vockel: None. (Val224_Thr227del) variant in the Nicastrin (NCSTN) gene. Results of the Delphi method for expert consensus are upcoming. Two state-of-the-art strategies, Z-score correlation across null-effect SNPs and LD score regression intercept, were widely applied to estimate phenotypic correlations. The CC genotype was the most frequent genotype in both RA patients (45.5%) and the controls (56.3%). verdez: None. Background: Patients and families with suspected, but genetically unexplained (unsolved) genetic tumour risk syndromes lack appropriate treatment and prevention, leading to preventable morbidity and mortality. These data have been coupled with WES and WGS data which allowed us to identify 10 genes (KIF1A, AGXT, PTCH1, RNF20, OR13C4, DNTT, SH3PXD2A, HEMGN, ABCA1, TPTE) harbouring coding variants, and 11 genes (HDAC3, SH3RF2, SLC36A2, LINC01933, WHRN, PAPPA, LCOR, R3HCC1L, BTRC, ADD3, CTBP2) harbouring non-coding variants, shared by all affected individuals, filtered for MAF and in-silico predictors. P20.012.C Lifestyle-dependent epigenetic signatures and the impact of lifestyle on epigenetic age acceleration Joanna Rudnicka 1, Rezvan Noorozi1, Aleksandra Pisarek1, Michał Boroń2, Aleksander Masny2, Bożena Woźniak2, Kamila Migacz-Gruszka3, EPIGENOME Consortium, Aneta Sitek4, Andrzej Ossowski5, Wojciech Branicki1,2, Magdalena Spólnicka2, Ewelina Pośpiech1 1Jagiellonian University, Kraków, Poland, 2Central Forensic Laboratory of the Police, Warszawa, Poland, 3Department of Dermatology, Collegium Medicum of the Jagiellonian University, Kraków, Poland, 4Department of Anthropology, Faculty of Biology and Environmental Protection, University of Łódź, Łódź, Poland, 5Department of Forensic Genetics, Pomeranian Medical University, Szczecin, Poland. The reported study was funded by RFBR, project number 20-015-00397. Cantagrel: None. A.B. Sousa: None. Six families with PPN were selected having at least one affected member, positive neurological examination and pain questionnaire result with numerical rating score >=4. Orrico: None. Pintor: A. Conclusion: Our results identified several novel genes might be associated with smoking cessation in a Chinese population of Taiwan. K.C. Slep: None. Haack5, M. Conclusion: Since DCHS1 and FAT4 molecules form a receptor - ligand pair, we hypothesize that DCHS1 mutation may cause HS-like phenotype. Background: The causes and manifestations of congenital myopathy may be diverse. Nevertheless, the described DS adaptors' production methodology leads to a low ligation efficiency, which hinders their capability to work with limited amounts of input DNA such as cell-free DNA (cfDNA) samples. Karachanak-Yankova: None. Alahaideb: None. Burtin: None. The resulting testing approach is hypothesis-generating rather than hypothesis-testing and we propose represents the epistemology described in Biesecker, 2013 (Genomes Research 23:1051-1053) and a change of paradigm in genomic testing. Sznajer: None. Alves7, Carlo Di Lorenzo8,2 1Division of Genetic and Genomic Medicine, Nationwide Children's Hospital, Columbus, OH, USA, 2Department of Pediatrics, The Ohio State University, Columbus, OH, USA, 3Illumina Inc, San Diego, CA, USA, 4Nationwide Children's Hospital, Columbus, OH, USA, 5Pathology & Laboratory Medicine, Nationwide Children's Hospital, Columbus, OH, USA, 6Center for Gene Therapy, Abigail Wexner Research Institute, Nationwide Children's Hospital, Columbus, OH, USA, 7Department of Clinical Genetics, Erasmus University Medical Center, Rotterdam, Netherlands, 8Division of Pediatric Gastroenterology, Hepatology and Nutrition, Nationwide Children's Hospital, Columbus, OH, USA. In this study, molecular spectrum of 29 patients from 28 different families followed up with VWD type 3 was evaluated. Genomic DNA was isolated from peripheral blood leukocytes and next-generation sequencing (NGS) on the NextSeq500 Illumina platform was performed. We also observe that some of our genes and GPX4 are in the same co-expression network module within cortex and hippocampus tissue networks according to CoExp Web. We finally used transcription factor (TF) binding information to identify TFs with potential key role in nsCL/P etiology. Some patients with glycoform abnormality have none of the known molecular defects. Martínez-Martínez: None. Chromosome break points have not been determined. Fiegl: None. Introduction: Familial Multiple Lipomatosis (FML) is a rare condition, with an autosomal dominant pattern of inheritance, characterized by multiple subcutaneous lipomas. This is the first report of an unaffected male carrying a constitutional mutation in MECP2. Dissanayake4, N. Fedorov 1, Aitalina L. Methods: Thirty-four male and 64 female candidates had genetic counseling with a medical geneticist before donation. Thurm: None. Previous studies on ATXN2 showed that harbouring intermediate-length repeat expansions are significantly associated with the risk of ALS. Results: Treatment with sorafenib, VPA or metformin shown viability reduction in a dose-dependent fashion and the combination of 2 μM sorafenib, 4 mM VPA and 10 mM metformin showed strongest synergistic effect in the viability reduction. Scheiber Osteoporosis & Arthritis Center, Richmond, VA, USA. Clinical symptoms are delayed motor milestones like walking independently. The aim of this study was to evaluate clinical performance characteristics of the innovated GeneProof PCR assays intended for diagnostics of thrombophilic mutations in myCROBE® Fully Automated Instrument. When analyzing the duhlocus interaction between FTO re9939609 T> A and LPL Ser447Ter C>G, an antagonistic character is shown; between loci FTO re9939609 T> A and LPL Ser447Ter C> G, the nature of the interaction is synergistic, and with the LIPC-250 G>A polymorphism, it is antagonistic at loci FTO re9939609 T>A and LPL Ser447Ter C>G.Findings. In-frame skipping of exon 7 in ~50% of transcripts was found for MSH2 variant c.942+3A>T. It can result in ataxia, muscle weakness, dysmetria and other alterations on walk and movement. 19 (61%) patients on admission to the hospital have already received oxygen therapy (using an oxygen mask). Results: Despite the similarities between the three countries to offer NIPT as a second-tier screening tool, they exhibit differences with regard to their public discourses about prenatal genomics, screening policies, the risk-thresholds they use, professional regulations and laws. P20.014.A Functional characterization of variants in the 5UTR and promoter of PCK9 gene Ana Catarina Alves, Juliane Menezes, Rafael Fernandes, Luísa Romão, Mafalda Bourbon Instituto Nacional de Saúde, Lisboa, Portugal. Materials and methods: We ascertained a four-year old boy born to consanguineously married couple. The study also used semi-structured interviews to explore health professionals' experiences regarding the role of patients' religion and spirituality in coping and decision-making. Materials and Methods: Whole exome sequencing (WES) was performed on blood-derived DNA samples following each center's Next Generation Sequencing (NGS) pipeline. Kleinfinger: None. R.H.P. Wouters: None. In ~20% of cases conventional karyotyping is not possible because of absence of mitotic activity in chorion. P05.024.B Exosomal microRNA biosignature related with hypertension-associated kidney disease Ana Ortega 1, Javier Perez-Hernandez2, Olga Martinez-Arroyo1, Angela L. P01.024.D Transcriptome landscape of the human decidual cells Anastasia A. The meta-analysis revealed a significant association between circadian rhythm gene polymorphisms and MetS (OR = 1.19, 95% CI: 1.04-1.38, p = 0.013). Behavioral problems, anxiety and attention-deficit hyperactivity disorder appear to be common features of this condition. Still, the relatively high number of unsolved cases after routine NGS panel diagnostics prompted us to develop a structured analysis approach to allow exome-wide analysis within a diagnostic time-frame. Custom pipelines for sample analysis were developed and specific viral and control human regions and variant associated mutations were detected. BCL11A, USP34 and PEX13 genes of the 2p16.1-p15 region have been usually described as involved in neurodevelopmental delay in children with microduplication of 2p16.1-p15 region; these genes are not involved in this region, although our patient shares phenotypic characteristics with those affected by 2p16.1-p15microduplication. The COVID-19 pandemic has rendered in-person provision of genetic counseling impossible for prolonged periods in many countries, mandating a sudden shift to remote delivery. Serum IgA and CD8 levels were significantly lower in patients than in controls (p 0,00685; p 0,000656 respectively). Our study highlights the importance of genetic testing in the differential diagnosis and early management of FXTAS. Activity tests in Caco-2 intestinal cells show strong cooperative effects of the four predicted introns on CFTR promoter activity. About 100 gene-partners of KMT2A have been discovered so far, but many are still unknown. Our application of array comparative genomic hybridization (aCGH) and next generation sequencing (NGS) has shown that 10-15% of oocyte aneuploidy is in fact premeiotic (PM) and present in the early embryo, leading to a risk of an aneuploid conception in adult life irrespective of age. Results: Two previously described de novo heterozygous pathogenic variants in the ACTG2 /(c.119G>A p.(Arg40His) and c.770G>A (p.Arg257His)/ where detected. Selected individuals were analyzed using various genetic approaches. J.A. Mayr: None. Because the known germline pathogenic variants are mostly related to homologous recombination repair (HR) pathway genes, it has been hypothesized that variants in unknown genes or variants of uncertain significance that lead to HR deficiency (HRD) can contribute to a large fraction of the unsolved cases. For phenylketonuria DCFs were 0.0226 and 0.0239; for alpha-1 antitrypsin deficiency - 0.0436 and 0.0497; for SNHS - 0.0576 and 0.0696, respectively. We performed WES analysis of 100 patients with either early-onset and/or familial PD, consecutively referred from 2014 to 2021 to our center from Slovenia, Croatia and Serbia. Esophageal cancer is one of the most common types of cancer worldwide and sixth in Kazakhstan. Conclusions: Results show that PGT-M was performed for 94 different genes during 2014-2017 while it reaches 323 in 2021. A male patient was carrying 2 maternally inherited variants, one hemizygous in BCOR and one heterozygous in MYO9B, genes associated to cognitive and behaviour impairment. Ogilvie: None. Objective: Genomic sequencing and clinical genomics have demonstrated substantial subsets of atypical and/or severe disease presentations result from multilocus pathogenic variation (MPV) causing blended phenotypes. Leutner: None. Tumiene: None. As conventional laboratory mice are inherently resistant to SARS-CoV-2 infection, various strategies have been adapted to deploy infection-permissive mouse models with a range of viral tropisms and COVID-19 clinical features. M.H. van den Boogaard: None. Clark: B. Materials and Methods: The data of ophthalmological examination and molecular genetic analysis of 83 patients from 0 to 18 years old were analyzed. Urioste: None. Introduction: Membrane trafficking is an essential process in eukaryotic cells responsible for protein transport and processing. Following a UAA 'AND' command, we added nucleotide coding for the 'S' protein associated with B1.1.7 variant, to include N501Y and E484K variants to the Wuhan-Hu-1 coronavirus, followed by a second UAA, then followed by 3' terminal end of CD8A mRNA and a poly adenine tail. The rearrangement breakpoints were refined to the base-pair level in all affected individuals. Hammarsjö: None. Lelliott6, Christel Thauvin-Robinet1,2,21, Christophe Philippe1,2, Binnaz Yalcin2, Laurence Faivre2,3,7 1Unité Fonctionnelle Innovation en Diagnostic génomique des maladies rares, FHU-TRANSLAD, CHU Dijon Bourgogne, Dijon, France, 2UMR1231 GAD, Inserm - Université Bourgogne-Franche Comté, Dijon, France, 3European Reference Network, ERN ITHACA, Dijon, France, 4Center for Integrative Genomics, University of Lausanne, Lausanne, Switzerland, 5IGBMC, UMR7104, Inserm, U964, Illkirsch, France, 6Wellcome Sanger Institute, Hinxton, Cambridge, United Kingdom, 7Centre de Référence Maladies Rares « Anomalies du développement et syndromes malformatifs », Centre de Génétique, FHU-TRANSLAD et Institut GIMI, CHU Dijon Bourgogne, Dijon, France, 8Cincinnati Children's Hospital Medical Center, University of Cincinnati School of Medicine, Cincinnati, OH, USA, 9Instituto de Genética Médica y Molecular (INGEMM), Hospital Universitario La Paz, Universidad Autónoma de Madrid, IdiPAZ, Madrid, Spain, 10Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER, U753), Instituto Carlos III, Madrid, Spain, 11European Reference Network, ERN ITHACA, Madrid, Spain, 12Département de génétique médicale, CHU Timone enfants, AP-HM, Marseille, France, 13Laboratory for Neurofibromatosis Research, Department of Human Genetics, KU Leuven University Hospital, Leuven, Belgium, 14Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA, 15Baylor Genetics Laboratories, Houston, TX, USA, 16Genetica Medica, Azienda Ospedaliera Universitaria Senese, Siena, Italy, 17Medical Genetics, University of Siena, Siena, Italy, 18Med Biotech Hub and Competence Center, Department of Medical Biotechnologies, University of Siena, Siena, Italy, 19Dipartimento di Medicina Molecolare e dello Sviluppo, Universita' degli Studi di Siena, Siena, Italy, 20U.O.C. Pediatria, Azienda Ospedaliera Universitaria Senese, Siena, Italy, 21Centre de Référence Déficiences Intellectuelles de Causes Rares, FHU-TRANSLAD, CHU Dijon Bourgogne, Dijon, France. M.S. Mustak: None. E.V. Filatova: A. Geoffroy: None. Ö. Alternative splicing in PPCD1 vs controls was further identified for ESRP1 targets, CD44 and FGFR2. Fortuna: None. Our findings expand the clinical phenotype associated with FAM111A mutations beyond KCS2 and GCLEB and, consistent with FAM111A interaction with the Proliferating cell nuclear antigen (PCNA) and its re-localization to chromatin during the S-phase, suggest a role of this gene as chromatin replication factor and of the present associated phenotype as a novel coesinopathy. Taking into account the overall symptoms and the repeatability of the phenotype, we suggest delineating a separate disease entity and support the acronym FIPWE. However, many psychiatric and neurological disorders are genetically correlated with behavioral and cognitive traits that have been the focus of large GWAS. However, total uptake stabilized at 46% for both years of TRIDENT-2. Balis: None. A monogenetic cause can be identified in 5% to 10% of patients. (Gly2428Arg) in exon 44 of FLNA, mother is a carrier and father has wild type allele. Materials and methods: Separation of two groups of mice of at least n = 10 on a standard diet and on a KD +/- Vitamin D. Conclusions: EV-enriched miR-625-3p could serve as a prognostic biomarker in MM and could contribute to a more personalized treatment in these patients. Research and diagnostics in human, with chromosomes in focus, were originally designated as "cytogenetics". Materials and Methods: A clinical case of methylmalonic acidemia. Materials and Methods: Data was collected by interrogation of departmental databases and molecular genetic reports at Children's Health Ireland, Crumlin, the Mater Misericordiae University Hospital and Tallaght University Hospital. Rusu: None. Feenstra: None. Rare genetic disorders leading to phosphate deficiency are associated with defective mineralization, but it is unclear whether serum phosphate is related to bone mineral density (BMD) in the wider population. However, future studies are necessary for confirmation of rs897543876 pathogenic role. A 32-year-old woman was referred for prenatal diagnosis for cervical incompetence. In this report we demonstrated a successful treatment with oral uridine in term of mobility, consciousness, communication, and cessation of seizure rendering this disorder as one of the few treatable neurometabolic diseases. Conclusion: NIPT implementation in Moscow demonstrates high efficiency and accuracy. P02.068.A Biallelic pathogenic variants in COL9A3 confirm autosomal recessive stickler syndrome Aboulfazl Rad 1, Maryam Najafi2, Fatemeh Suri3, Stephen Loum1, Ehsan Ghayoor Karimiani4, David Murphy5, Mohammad Doosti4, Narsis Daftarian6, Paria Najarzadeh Torbati4, Afrooz Moghaddasi3, Hamid Ahmadieh3, Mohsen Rajati7, Narges Hashemi8, Barbara Vona1, Miriam Schmidts9 1Department of Otorhinolaryngology, Head and Neck Surgery, Tübingen, Germany, 23Pediatric Genetics Divison, Center for Pediatrics and Adolescent Medicine, University Hospital Freiburg, Freiburg University Faculty of Medicine, Mathildenstrasse 1, 79106 Freiburg, Germany, Freiburg, Germany, 3Ophthalmic Research Center, Research Institute for Ophthalmology and Vision Science, Shahid Beheshti University of Medical Sciences, Tehran, Iran, Tehran, Iran, Islamic Republic of, 4Department of Molecular Genetics, Next Generation Genetic Polyclinic, Mashhad 009851, Iran, Mashhad, Iran, Islamic Republic of, 5Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, University College London, United Kingdom, London, United Kingdom, 6Ocular Tissue Engineering Research Center, Research Institute for Ophthalmology and Vision Science, Shahid Beheshti University of Medical Sciences, Tehran, Iran, Tehran, Iran, Islamic Republic of, 7Associate professor of Otorhinolaryngology, Ghaem Hospital, Sinus and Surgical Endoscopic Research Center, Department of Otorhinolaryngology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran, Mashhad, Iran, Islamic Republic of, 8Department of Pediatric Neurology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran, Mashhad, Iran, Islamic Republic of, 9Pediatric Genetics Divison, Center for Pediatrics and Adolescent Medicine, University Hospital Freiburg, Freiburg University Faculty of Medicine, Mathildenstrasse 1, 79106 Freiburg, Germany, Freiburg, Germany. H.J. Byers: None. SNPs distributed across all exons. Multivariable MR was conducted to estimate the independent effect of phosphate on BMD conditioning on calcium. The search strategy was piloted on PubMed. Material and methods: solida-core relies on the Snakemake framework. We trained a deep convolutional neural network to classify peaks within the raw signal and developed assay-specific logic to translate peak calls into sample genotypes. This strategy can be applied to any disease provided that the molecular cause is a primary nonsense mutation. Of the 17 novel variants seven were classified as "likely pathogenic", four as "likely benign"and six remained VUS. rs1360780 (C->T) was genotyped using Taqman SNP genotyping assay. In this study, our goal was to determine the pathogenicity of a novel MLH1 in-frame deletion variant MLH1_del746-749: LRG_216t1:c.2236_2247delCTGCCTGATCTA p.(Leu746_Leu749del). Alotaibi: None. Studying the genome of centenarians may give insights into the molecular mechanisms underlying extreme human longevity and the escape of age-related diseases. Among In theise 52 genes only 14 had beenve scored to date by ClinGen. The European Hereditary Tumour Group (EHTG) commissioned an update of the previous guideline from 2010 (Beggs et al. First classified into three types (types I, II, and III) based on biochemical manifestations, it was later reclassified into types I (CTLN1, MIM# 215700) and II (CTLN2, MIM# 603471) based on molecular pathogenesis. This is a group of multisystem conditions characterized by skeletal dysplasia and various extra-skeletal features. Conclusions: These findings are consistent with the growing evidence implicating inflammatory responses in the aetiology and progression of PD. Even if they are considered latent in the majority of cases, these infections can trigger some degree of local or systemic immune response, resulting in a chronic state of low-grade inflammation. P12.075.C High sensitivity detection of endometrial cancer-associated genetic variants in minimally-invasive gynecological samples Fátima Marín* 1, Beatriz Pelegrina*2, Sònia Paytubi*2, Ferran Briansó3,4, Paula Peremiquel2, Jon Frias2, Yolanda Benavente2, José Manuel Martínez5, Marc Barahona5, Sergi Fernández5, Alba Zanca6, Nuria Baixeras6, August Vidal6, Axel Rodríguez6, Júlia Canet1, Álvaro Carmona2, Javier de Francisco7, Victor Caño7, Francesc Xavier Bosch2, Silvia de Sanjosé8, Jordi Ponce5, Gabriel Capellá1, Xavier Matias-Guiu6, Joan Brunet1,9, Laia Alemany2, Marta Pineda*1, Laura Costas*2 1Hereditary Cancer Program, Catalan Institute of Oncology, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), ONCOBELL Program, CIBERONC, L'Hospitalet de LLobregat, Spain, 2Cancer Epidemiology Research Programme, Catalan Institute of Oncology, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), CIBERESP, L'Hospitalet de LLobregat, Spain, 3Department of Genetics, Microbiology and Statistics, Universitat de Barcelona, Barcelona, Spain, 4Roche Diagnostics, Sant Cugat del Vallès, Spain, 5Department of Gynecology, Hospital Universitari de Bellvitge, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), L'Hospitalet de LLobregat, Spain, 6Pathology, Hospital Universitari de Bellvitge, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), L'Hospitalet de LLobregat, Spain, 7Department of Anesthesiology. Furthermore, the presence of pulmonary thromboembolism with lymphocytic myocarditis prompted the search of cardiotropic viruses within the myocardium. Faletra: None. L.C. Melchior: None. Vasilyeva, Vitaly V. Introduction: Genetic consultations are often centralized over a large area, sometimes requiring patients to travel long distances. Results: In September 2019, the patient was found metastatic adenocarcinoma of lung in right upper and right lower lobes. Studies in ALL show that SNP microarray can reveal a copy-neutral loss of heterozygosity (CN-LOH) of disomic chromosome in hyperdiploid karyotype. Association study focused on three major clinical features: cutaneous (cNFs), subcutaneous (scNFs), and plexiform (pNFs) neurofibromas. The most recurring genes are CELSR1 (8 patients), FREM2 (5), GLDC (4) or APAF1 (3). P03.006.B Impact of human genetic variants on C-Reactive Protein levels and acute appendicitis Isis Ricaño-Ponce 1, Toon Peeters1,2,3, Vasiliki Matzaraki1, Mihai Netea1,4, Inge Gyssens1,2,3, Vinod Kumar1,5 1Department of Internal Medicine and Radboud Center for Infectious Diseases, Radboud University Medical Center, NIJMEGEN, Netherlands, 2Department of Infectious Diseases & Immunity, Jessa Hospital, Hasselt, Belgium, 3Faculty of Medicine and Life Sciences, Hasselt University, Hasselt, Belgium, 4Human Genomics Laboratory, Craiova University of Medicine and Pharmacy, Craiova, Romania, 5University of Groningen, University Medical Center Groningen, Department of Genetics, Groningen, Netherlands. Genes were selected based on interactions with hs-CRP, MMP-9 and IL-1β markers (37 genes, 382 SNPs). P07.004.D Diagnostic performance of NGS panel genetic testing in patients suspected for autoinflammatory syndrome Gorjan Milanovski 1, Meri Kirijas1, Boban Dobrevski1, Teodora Brnjarchevska Blazevska1, Olivija Efinska Mladenovska1, Olgica Sibinovska1, Todor Arsov1, Katarina Stavrikj2, Kristina Mironska2, Beti Gjurkova2, Aleksandar Petlichkovski1 1Ss. Cyril and Methodius University in Skopje, Faculty of Medicine-Skopje, Institute of Immunobiology and Human Genetics, Skopje, Macedonia, The Former Yugoslav Republic of, 2Ss. Cyril and Methodius University in Skopje, Faculty of Medicine-Skopje, PHI University Clinic for child diseases, Skopje, Macedonia, The Former Yugoslav Republic of. Materials and Methods: The study group included 31 patients (15 women and 16 men) with diagnosis "viral COVID-19 pneumonia" treated at the intensive care unit. Karyotype: mos 49,XX,+inv dup(15)(q11.2)x2,+r(1)(p1?1.2q22.?1)[5]/48,XX,+inv dup(15)(q11.2)x2[35]. Damon: None. M.F. Brandao-Gois: None. Although continental genetic ancestry has substantial power for prediction of pigmentation in Latin Americans, the inclusion of pigmentation SNPs increases prediction accuracy considerably, particularly for skin color. Recently we have shown that the ARID1B phenotype can include normal IQ values, suggesting that a pathogenic variant may be inherited from a very mildy affected parent. Bejo: None. Materials and methods: A total of 764 adults with obesity from seven European countries consumed a liquid high fat meal. Š. Loum: None. P03.048.D Genome wide association study of type 2 diabetes complications in population of Latvia Raitis Peculis 1, Monta Ustinova1, Raimonds Rescenko1, Vita Rovite1, Linda Zaharenko1, Ilze Elbere1, Laila Silamikele1, Ilze Konrade2,1, Jelizaveta Sokolovska3, Valdis Pirags3,1, Janis Klovins1 1Latvian Biomedical Research and Study Centre, Riga, Latvia, 2Faculty of Medicine, Riga Stradins University, Riga, Latvia, 3Faculty of Medicine, University of Latvia, Riga, Latvia. This led to a genome-wide, quantitative map of enhancer activity of relevance for neurodevelopmental disorders. J.M.A. Pickl: None. Furthermore, musculoskeletal disorders and cardiovascular disease were genetically correlated with POP. His head circumference was 48 cm (-6,34 SD). Introduction: We present a sudden cardiac death (SCD) case resolved by post mortem genotyping through clinical-laboratory geneticists' collaboration employing new and traditional genomic technologies. To date almost 200 pathogenic variants are annotated as splice-affecting, many of which locate outside of the canonical splice sites dinucleotides. In all but one family, bi-allelic protein truncating variants were identified in YIF1B, with only a single bi-allelic missense mutation assumed to be causative. Haeusler: None. P14.022.D More accurate penetrance estimates for neurosusceptibility loci lead to significantly reduced penetrance estimates Shuxiang Goh 1, Rhys Bowden2, Mark Pinese3, Edwin Kirk1 1Sydney Children's Hospital, Sydney, Australia, 2Monash University, Melbourne, Australia, 3University of New South Wales, Sydney, Australia. Mirecka-Rola: None. Wilsnack: None. Future translation into additional languages is also being considered. Brain magnetic resonance image (MRI) was normal and electroencephalogram (EEG) showed spike and sharp-wave complexes emerging in the left hemisphere parietooccipital areas which paroxysmally generalized. General toxicity and locomotor function were evaluated via developmental lethality and negative geotaxis climbing assays. LoFTK enables the identification of genes that are inactive in one or two copies and provides summary statistics for downstream analyses. The further solved TBMN cases carried heterozygous causative variants in COL4A3, COL4A4 or COL4A5 (female). Vancollie6, Mathys Weber2,7, Carlos Prada8, Alexis Overs1,2, María Palomares-Bralo9,10,11, Fernando Santos-Simarro9,10,11, Marta Pacio-Míguez11, Tiffany Busa12, Eric Legius13, Carlos A. There is a large variability in the functional outcome after a stroke, partially regulated by genetic factors. R.M. Regojo: None. Borgatti: None. The COVID19 pandemic, has made the delivery of urgent Genetic ward consultations extremely challenging. In addition to common symptoms such as hypotonia, intellectual disability/developmental delay, and seizures, individuals with PIGG variants of null or severely decreased activity showed cerebellar abnormalities, neurological manifestations, and mitochondrial dysfunction, a feature increasingly recognized in IGDs. Individuals with mildly decreased activity variants showed autism spectrum disorder. Vitale: None. It is classified into two types: liver PHK deficiency and muscle PHK deficiency, and is caused by mutations in PHKA1, PHKA2, PHKB and PHKG2 genes. No exception to this pathogenetic model was found. Results: In NCCN-HBOC genes 466 PVs and in nonNCCN-HBOC FA genes 37 PVs were identified. Lai2, Maggie Brett2, Ganeshwaran H. Automated genotyping and QC logic was bundled into push-button reporting software for use with the PCR/CE assay. Moreover, XPG-Asp1104His was associated with Luminal-A subtype and PR-positivity(p = 0.042, p = 0.021, respectively). Chevarin: None. Graham15, Parul Jayakar16, Barry Byrne17, Bat El Bar-Aluma4,5, Yael Haberman4,5,18, Amir Szeinberg4,5, Hesham M. J.E. Blume: A. However, compared to wild type NMDAR, mutated one is less expressed at the cell surface and display a reduced NMDA current amplitude with higher sensitivity to magnesium blockade. mtDNA Hi-C data of healthy and COVID-19 patient samples also demonstrated a high-density region in the expected contact zone. P19.058.B Preliminary study of association of tuberculosis forms with polymorphisms in IFN-γ, IL-1β, NOS2, MARCO and TLR8 genes Ainur Akhmetova 1,2, Ulan Kozhamkulov1, Dauren Yerezhepov1, Ainur Akilzhanova1,2 1Laboratory of Genomic and Personalized Medicine, National Laboratory Astana, Nazarbayev University, Nur-Sultan, Kazakhstan, 2Department of General Biology and Genomics, L.N.Gumilyov Eurasian National University, Nur-Sultan, Kazakhstan. Willing: None. Deneufbourg: None. The second mother showed a truncating homozygous variant in the NLRP2 gene (p.Gln602ter). Zhan: None. With limited time to test individual pharmacogenomics markers, population pharmacogenomics could help in predicting a higher risk of developing adverse reactions and treatment failure in COVID-19 patients. Two patients showed classical DMD phenotype, with loss of ambulation within 13-year-old while in the other four patients ambulation was lost >age 15. We evaluated mtDNA deletions by long range PCR and ddPCR, with characterization of deletion breakpoints, and mtDNA copy number by qPCR. Introduction: Despite the increasing global burden of neurological disorders, there is a lack of effective diagnostic and therapeutic biomarkers. We reanalysed genetic data from a published ALS GWAS (N = 36,052) to assess sex differences in genetic architecture of the disease. P06.038.C A novel mutation of PDP1 gene in a pediatric patient Flavia Anne-Elise Szekely 1, Adela Chirita-Emandi2, Cristian Zimbru3, Nicoleta Andreescu2, Maria Puiu2 1Emergency Clinical County Hospital "Pius Branzeu", Timisoara, Romania, 2Center of Genomic Medicine, University of Medicine and Pharmacy "Victor Babes", Regional Center of Medical Genetics Timis, Clinical Emergency Hospital for Children "Louis Turcanu", part of ERN ITHACA, Timisoara, Romania, 3Center of Genomic Medicine, University of Medicine and Pharmacy "Victor Babes", 4. Esen: None. Anthonymuthu1,3,4,5, Hülya Bayir1,3,4,5, Jerry Vockley1,6 1University of Pittsburgh, Pittsburgh, PA, USA, 2UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, USA, 3Children's Neuroscience Institute, UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, USA, 4Safar Center for Resuscitation Research, University of Pittsburgh, Pittsburgh, PA, USA, 5Center for Free Radical and Antioxidant Health, University of Pittsburgh, Pittsburgh, PA, USA, 6Center for Rare Disease Therapy, UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, USA. Pfeifer: None. Aim: Using RT-PCR methodology in order to verify the accuracy of some Ag RDTs. Materials and Methods: From about 63.000 samples tested in our laboratory until now, our study focused on 31 patients from a prison tested positive by Ag RDTs. All patients were men aged between 19-71. Burchard*5,6, Maria Pino-Yanes *1,7,8 1Genomics and Health Group, Department of Biochemistry, Microbiology, Cell Biology and Genetics, Universidad de La Laguna, San Cristóbal de La Laguna, Tenerife, Spain, 2Instituto Universitario de Enfermedades Tropicales y Salud Pública de Canarias (IUETSPC), Universidad de La Laguna, San Cristóbal de La Laguna, Tenerife, Spain, 3Bay Area Pediatrics, Oakland, CA, USA, 4Centro de Neumología Pediátrica, San Juan, PR, USA, 5Department of Bioengineering and Therapeutic Sciences, University of California San Francisco, San Francisco, CA, USA, 6Department of Medicine, University of California San Francisco, San Francisco, CA,

USA, 7Instituto de Tecnologías Biomédicas (ITB), Universidad de La Laguna, San Cristobal de La Laguna, Tenerife, Spain, 8CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain. Gradstein: None. J.A. Rosenfeld: None. Kremer4, Johannes Bras5, Huib Caron4, Rachael Windsor6, Jeremy Whelan6, Ana Patiño-García7, Anna González-Neira8, Geoff McCowage9, Sumanth Nagabushan9, Federica Saletta9, Daniel Catchpoole9, Henk-Jan Guchelaar2, Han G. Secondly in a 30-week old fetus with severe growth retardation and duodenal atresia a de novo p.Pro805Leu KCNMA1 mutation was identified. Formankova: None. - to visualize their own data, users don't need to upload it to a tgg-viewer server or create a user account. We report a case diagnosed to have LPI using a Next Generation Sequencing (NGS) panel and evaluate the utility of reverse phenotyping. This work was supported by a grant from the President of the Russian Federation for young scientists - candidates of science MK-1228.2021.1.4. M. Loss of FKBP6, however, did not affect the localization of these factors. Harris1, Elizabeth Lewis1, Ala Abid1, Peggy Hall3, James Hayhurst1,2, Lucia A. P18.026.D Extracellular vesicle enriched miRNAs as prognostic biomarkers in malignant mesothelioma Katja Goricar 1, Marija Holcar1, Nina Mavec1, Viljem Kovac2, Metka Lenassi1, Vita Dolzan1 1Institute of Biochemistry and Molecular Genetics, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia, 2Institute of Oncology Ljubljana, Ljubljana, Slovenia. Meems-Veldhuis, Henny H. Vandecruys: None. Drug - related Q -T trait prolongation is a common problem in several clinical settings: the admnistration of many drugs, ranging from antidepressants to mood modulating drugs, can be responsible for such phenotype, according to current knowledge. Following this finding, the MAGEL2 gene was added to our standard neuromuscular panel. Bujosa: None. M.D.O. Ribeiro: A. P12.172.D Searching for germinal mutations of TET2, KMT2D, KDM6B, IDH1 and SETD2 epigenetic genes in Polish prostate cancer patients - preliminary results Marta Karolina Heise 1, Piotr Jarzemski2, Aneta Bąk1, Anna Junkiert-Czarnecka1, Maria Pilarska-Deltow1, Maciej Borysiak2, Beata Pilarska2, Olga Haus1 1Department of Clinical Genetics, Faculty of Medicine, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University, Toruń, Poland, 2Department of Urology, Jan Biziel University Hospital, Bydgoszcz, Poland. However, the counsellor's role extends beyond merely identifying genetic abnormalities. Butenko: None. Montillot: None. In contrast, after 8Gy the genes were enriched in cell cycle and G protein-coupled receptor signalling process. Bernert: None. Eussen3, Annelies de Klein3, Fernanda S. Smits 1, Rachel Schot1, Martina Wilke1, Marjon van Slegtenhorst1, Brahim Tabarki2, Amal Alhashem2, Antonio Romito3, Aida M. Conclusion: This is the first report to describe homozygosity for an in-frame deletion in B3GAT3 (p.(Leu21del)) and the first adult phenotype described. Conclusions: Our results demonstrate that use of the PRS-313 in the BOADICEA model in genetically unexplained breast cancer families and carriers of moderate breast cancer risk variants can potentially influence clinical management in substantial proportions of counselees. Number Percentage of women that would change breast cancer risk classification after addition of PRS-313 to BOADICEA IKNL guideline IKNL guideline NICE guideline NCCN guideline All cases 3,925 34 36 27 All controls 3,479 5 11 5 Cases with gene panel result Non-carriers 2,313 34 34 27 ATM carriers 40 23 23 0 CHEK2 carriers 164 27 24 7 PALB2 carriers 10 0 0 0 I.M.M. Lakeman: None. Timeva: None. The aim of the study was to compare mtDNA polymorphism in the people living at different heights. Guntekin Ergun: None. Martí: None. Mazzucotelli: None. Additionally she had right vertebral artery tortuosity, a history of gastric hemorrhage from Dieulafoy's ulcer, hand osteoarthritis, osteoporosis (repeated spontaneous metatarsal fractures), hypermobile joints (Beighton score 4), uvula aplasia, velvety and translucent skin with visible underlying veins. The atypical presentation of CF with liver involvement is very rare and lethal in an infant. Supported by RSF №19-15-00108. P05.054.D Telomere length in the pre- and postoperative period of coronary artery disease patients Maxim Aidarovich Asanov, Alena Olegovna Poddubnyak, Anastasia Valerievna Ponasenko Research Institute for Complex Issues of Cardiovascular Diseases, Kemerovo, Russian Federation. P17.025.D ILIAD project: the ERN-ITHACA online registry of rare diseases with intellectual disability and anomalies of development Morris Swertz 1, Klea Vyshka2,3, Fernanda de Andrade1, Joeri Van Der Velde1, Lennart Johansson1, Dieuwke Prins1, Jill Clayton-Smith4,5, Dorica Dan6, Sofia Douzgou Houge4,7, Laurence Faivre8,9, Tiziana Franchin10, Andrew Green11, Raoul Hennekam12, Anne Hugon2, Sylvia Huisman12, Helger Ijntema13, Tjitske Kleefstra14, David Koolen14, Andrea Manunta15, Jukka Moilanen16, Giovanni Mosiello17, Sarra Selatnia2, Mahsa Shabani18, Ammi Sundqvist19, Marco Tartaglia20, Zeynep Tümer21, Birute Tumiene22, Lisenka Vissers13,23, Dagmar Wieczorek24, Giuseppe Zampino25, Alessandra Renieri26,27,28, Alain Verloes2,29 1Dept. Estrogen is the primary female sex hormone and plays an important role for skeletal health in both sexes. Harper: None. The 63.2% (60/95) of patients were males while 36.8% (35/95) were females. However, its implication in human disease has not been confirmed so far. Naret: None. Matulevičienė: None. Brain CT showed cerebellar atrophy and expression of prominent cisterns, cerebellar and vermian folia, given clove leaf-like appearance consistent with hereditary cerebellar degeneration. Results: In 207 families where a pathogenic/likely pathogenic variant was detected, 1422 relatives had predictive testing. S Winsvold: None. Conclusion: Cytoplasmic linker-associated protein 1 (CLASP1) belongs to a group of proteins known as CLASPs which are non-motor microtubule-associated proteins that interact with CLIPs (Cap-Gly Domain-containing linker protein), a member of the microtubule plus-end tracking protein family. V.V. Kunitsa: None. One case was initially diagnosed with stage IV CRC; the second developed metastatic disease 2 years post-metachronous CRC. Yudkin, Anna K. Background and Objectives: Chronic widespread musculoskeletal pain (CWP) is a symptom of fibromyalgia and a complex trait with poorly understood pathogenesis. An integrated bioinformatics pipeline with a visual user interface provides variant calling, functional annotation of variants, presence in population, phenotype and oncology databases including ClinVar, COSMIC etc, and predicted protein effect. All patients showed typical skin manifestations at inborn or during the neonatal period. Genomic DNA was extracted from peripheral blood leukocytes by DNA salting out procedure. F.M. Nedelea: None. From affected 45 individuals, homozygous forms were detected in 33.3% (M694V 31.1%, M680I(G/C) 2.2%) of the cases. Faculty of Medicine and Pharmacy, Mohammed V University, Rabat, Morocco, 2Department of Medical Genetics, National Institute of Health, Rabat, Morocco, 3Pediatric practice, Meknes, Morocco. Translocations can disrupt functional parts of the genome and have implications for protein production with phenotypic consequences. Introduction: Cell-free fetal DNA analysis is now performed routinely for aneuploidy screening, fetal RhD genotyping or sex determination. Goverde: None. Conclusions: Our data shows significant improvements for both the primary endpoint (empowerment) and secondary endpoints (knowledge, depression, anxiety). The knockdown of TRAF2 increased NF-κB activity in healthy lung pericytes, which correlated with a significant increase in proliferation. Valdmanis University of Washington, Seattle, WA, USA. Seizures were described once in an individual additionally carrying a de novo 15q13.3 microdeletion. Pini: None. Sensi: None. Exon 2 duplication is the most frequent duplication and is associated with variable phenotypes, ranging from mild to severe. Hereby, we report two additional cases with pathogenic variants in ACTG2, and a case where a pathogenic variant in KCNMA1 was found. SNP-array testing was performed, with preliminary diagnosis of syndromic microphthalmia, revealing a deletion encompassing NHS. The most sensitive and reliable method for TCR/BCR profiling is DNA based target multiplex PCR in combination with high-throughput sequencing. The software was able to process each case in less than 15 minutes when running on a desktop computer. Blaak: None. 26/90 were classified as "not solved" (original report: 7/90), due to inconclusive results on variant (11/90), on genotype (12/90) or both variant and genotype level (3/90). Results: WES detected 12 pathogenic variants, 3 likely pathogenic variants, and 3 variants of uncertain significance (VUS) from this cohort. This research was conducted within the project which has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 754432 and the Polish Ministry of Science and Higher Education, from financial resources for science in 2018-2023 granted for the implementation of an international co-financed project. Conclusions: In our cohort of patients CNV-mediated double-hit mechanisms seem to play a relevant role in NDDs, helping to elucidate complex phenotypes. Demographic data including clinical role and (regional) health board was also collected along with free text responses. There are several polymorphisms being discovered every day that could explain the HbF variation between different geographic regions. Hobart: None. Sincan: None. Ezquerro: None. The median age at first TUS was 37 years (interquartile range (IQR): 24-43) with a median follow-up of 3 years (IQR: 1-5). Introduction: Loss-of-function variants in SETD5 gene cause the core phenotype of 3p25.3 microdeletion syndrome characterized by intellectual disability/autism, slow growth, dysmorphic features and malformations such as postaxial polydactyly, heart condition and genitourinary anomalies. In mouse embryonic stem cells, both proteins have been shown to physically interact at the molecular level. FGFR2, FGFR3, FGFR1, TWIST1 and EFNB1 are major causative genes of genetic syndromes associated with craniosynostosis. Little is known about the mechanisms of their action. To maximize healthy baby outcomes PCR-free Whoe Genome Sequencing (WGS)is desired, but nearly impossible due to the limited amount and quality of samples. The implications of novel lncRNAs for pathogenesis and development of potential diagnostics will be further studied.Work was supported by grant of the Science Committee of the Ministry of Education and Science of the Republic of Kazakhstan, #AP09058660, and NU CRP grant 021220CRP2222. Methods: The patient who had no history of hypertension was rehospitalized after surgery for aortic dissection, he presented with aortic root aneurysm and aorta dilates in many parts with no other abnormal signs. DNA samples were analyzed by Sanger sequencing in the region spanning rs# 1126477 and rs#1126478 variants. Pageot: None. Bieth: None. We present data relating to a child investigated for global developmental delay, intellectual disability, malformations of the heart and great vessels, autistic traits, and attention deficit hyperactivity disorder. Wilson2, Francesca Picco1, Daniel Medina-Cano1, Nami Altin1, Nadia Bahi-Buisson1, Catherine Fossoud3, Fabienne Giuliano4, Laurence Colleaux1, Lydie Burglen1, Joseph G. P12.155.C Weighted gene co-expression network analysis of ovarian cancer transcriptional profile and its relations to stemness Anna Erol 1, Magdalena Niemira1, Karolina Chwiałkowska2, Anna Szałkowska1, Agnieszka Bielska1, Justyna Raczkowska1, Gabriela Sokołowska1, Iwona Sidorkiewicz1, Katarzyna Doroszko1, Katarzyna Doroszko1, Patrycja Modzelewska3, Mirosław Kwaśniewski2, Joanna Reszeć3, Jacek Szamatowicz4, Paweł Knapp5, Marcin Moniuszko6, Adam Krętowski1,7 1Clinical Research Centre, Medical University of Bialystok, Bialystok, Poland, 2Centre for Bioinformatics and Data Analysis, Medical University of Bialystok, Bialystok, Poland, 3Department of Medical Pathomorphology, Medical University of Bialystok, Bialystok, Poland, 4Department of Gynecology and Gynecological Oncology, Medical University of Bialystok, Bialystok, Poland, 5University Oncology Centre, Medical University of Bialystok, Bialystok, Poland, 6Department of Regenerative Medicine and Immune Regulation, Medical University of Bialystok, Bialystok, Poland, 77Department of Endocrinology, Diabetology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland. Martinelli: None. Pavlovic: None. The C allele and the CC genotype of rs11638944 presented at significantly lower frequencies in pseudoexfoliation patients ($p = 0.00754$, $OR = 0.50$; $p = 0.00876$, $OR = 0.35$, respectively). Results were analyzed with the Hereditary Angioedema Database Annotation (HADA) tool for causal variant prioritization. Babovskaya: None. M.H. Stoiber: A. Activating mutations in AKT3 gene are a rare cause of megalencephaly. P05.022.D Experience of an Italian reference laboratory for a rare disease: Hereditary Haemorragic Telangiectasia Carla Olivieri 1, Fabio Pagella2,3, Sara Plumitallo1, Uroš Hladnik4, Elisabetta Buscarini5, Elina Matti3, Anna Sbalchiero1, Guido Manfredi5, Giuseppe Spinozzi3, Elisabetta De Sando6, Sara Ugolini3, Cesare Danesino1 1General Biology and Medical Genetics Unit, Department of Molecular Medicine, University of Pavia, Pavia, Italy, 2Department of Otorhinolaryngology, University of Pavia, Pavia, Italy, 3Department of Otorhinolaryngology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, 4Unità di Genetica Istituto per le malattie rare "Mauro Baschirotto" - B.I.R.D. Foundation o.n.l.u.s., Costozza di Longare (VI), Italy, 5UOC Gastroenterologia-Centro di riferimento HHT, ASST Ospedale Maggiore di Crema, Crema (CR), Italy, 6Clinica Pediatrica, Fondazione IRCCS Policlinico San Matteoi, Pavia, Italy. Metabolic and mitochondrial DNA testing results were normal in both patients. The actual reason may not be cost, but the perceptual difference between selling the genomic screen versus presenting it as an option to improve patient care. Despite important clinical observations from over the last 25 years, LVNC etiology still remains unknown in 30-50% of cases. Wolfsberger1,2, Yaroslava Hasynets2, Olga T. Diagnostic variants were identified in 34 genes, with 44% identified in a single patient. Zhilina: None. Babushkina1, Natalia V. We aim to decipher the molecular mechanisms of knee osteoarthritis pathology in cartilage tissue. López Cuenca: None. Aaltonen: None. Pietrzyk: None. A.T. van der Ven: None. A tool for quality assessment, based on STROBE checklist, was applied. Correlations with clinical and laboratory parameters were performed. The parents in all three families did not have any STL-associated phenotypes. Genetics Department, Hospital Universitario La Paz, IdiPAZ, Madrid, Spain, 9Bioinformatics Section. Despite he had passed neonatal auditory screening, patient was consulted to ENT department again for hearing evaluation and diagnosed with moderate sensorineural type hearing loss. Sequencing was performed on the Illumina NextSeq 550 Sequencing System. Oelen: None. Winship: None. This approach may provide an estimate for the proportion of risk mediated by the X chromosome in individuals who develop AD with unilateral ancestral lineage, and is generalizable. P12.201.A High rate of (epi)genetic predisposing factors and an important role for DIS3L2 in a nationwide Wilms tumor cohort Janna A. Skrahina: None. It reduces isoform expression without preventing protein production and lowers Lp(a) by 14.0 mg/dL ([95%CI:15.3-12.6], $p = 4.82e-184$). P09.065.B Deep phenotyping of biallelic HACE1 variants Merope Griffin 1, Meena Balasubramanian2, Moira Blyth3, Abhijit Dixit1, Peter D. progenetix.orggithub.com/progenetix Q. Materials and methods: We use image-analysis and hydrodynamic calculations to show that epididymal CRISPs significantly influences sperm flagellar beating. Its predicted prevalence is 1-9/1.000.000. Introduction: Skraban-Deardorff syndrome (a disease related to variations in the WDR26 gene; OMIM #617616) was first described in a cohort of 15 individuals in 2017, no other cases have been described since. Introduction: Ritscher-Schinzel Syndrome (RSS) is a rare developmental disorder characterized by intellectual disability, cerebellar/brain-malformations, congenital heart defects and craniofacial abnormalities. In their experimental study, Borisov et al. el Haffaf: None. P12.042.B Search for markers and mechanisms of resistance to TKI therapy Elmira P. Most frequent pathogenic variants were c.2276G>T (p.Cys759Phe) in USH2A, c.847C>T (p.Arg283Ter) in CERKL and c.3260C>T (p.Ser1087Leu) in SNRNP200, identified in 12, 10 and 8 families respectively. Introduction: PPCD1 was recently shown to result from activating mutations in the promotor region of OVOL2. P17.067.B TGG-Viewer: Web-based Interactive Genome-wide Visualization of RNAseq Data Ben Weisburd Broad Institute, Cambridge, MA, USA. Bertini: None. Recently the cases of a Hungarian and an Anglo-Saxon pedigrees has been presented, who are affected by CYLD cutaneous syndrome (syn: Brooke-Spiegler syndrome), carry the same disease-causing mutation (c.2806C>T, p.Arg936X) of the cylindromatosis (CYLD) gene but exhibit striking differences in their phenotypes. N.J. Hafford-Tear: None. Antisense oligonucleotide-induced exon skipping can restore the mRNA reading frame and produce an internally deleted, yet functional dystrophin protein, as Exondys 51TM does in patients with confirmed DMD gene mutations amenable to exon 51 skipping. We aim to elaborate a simple clinical tool to identify patients with a greater probability of having a genetic disorder. Bayram: None. Introduction: Recent evidence from human and animal studies suggest that the immune system has an important role in Parkinson's disease (PD). P19.023.C An exome-wide analysis of natural genetic variation in the Canary Islands population Ana Díaz-de Usera 1, Luis A. P19.036.D Investigation of a nonsense mutation located in the complex KIV-2 copy number variation region of apolipoprotein(a) in 10,910 individuals Silvia Di Maio 1, Rebecca Grüneis1, Gertraud Streiter1, Claudia Lamina1, Manuel Maglione1, Sebastian Schoenherr1, Dietmar Öfner1, Barbara Thorand2, Annette Peters2,3, Kai-Uwe Eckardt4,5, Anna Köttgen6, Florian Kronenberg1, Stefan Coassin1 1Medical University of Innsbruck, Innsbruck, Austria, 2German Research Center for Environmental Health, Neuherberg, Germany, 3German Centre for Cardiovascular Research, Partner Site Munich Hearth Alliance, München, Germany, 4Friedrich-Alexander Universität Erlangen-Nürnberg, Erlangen, Germany, 5Universitätsmedizin Berlin, Berlin, Germany, 6University of Freiburg, Freiburg, Germany. Ramos: None. Battaloglu: None. Materials and methods: Two PJS patients belonging to the same family (father and daughter) were sequenced for the open reading frame of STK11 gene using the Sanger technique. Altisent: None. P09.046.C Whole exome sequencing as instrument of molecular diagnosis in children with developmental and epileptic encephalopathies Tatyana Kozhanova 1,2, Svetlana Zhilina1,2, Tatyana Mescheryakova1, Karina Osipova1, Sergey Ayvazyan1, Nikolay Zavadenko2, Andrey Prityko1,3 1Scientific and Practical Center of children medical care, Moscow, Russian Federation, 2Pirogov Russian National Research Medical University, Moscow, Russian Federation, 3Pirogov Russian National Research Medical University, Moscow, Russian Federation, Moscow, Russian Federation. Daughter of proband was observed for anxiety. Introduction: TGFBI-related corneal dystrophies are characterized by hyaline or amyloid deposition in the cornea due to missense mutations of TGFBI. Colonoscopic surveillance appears effective in reducing the cancer incidence in moderate and high-risk groups, presumably through polyp removal, thereby supporting continued use of the current guidance. To date, mostly truncating variants have been reported. Silver-Russell syndrome (SRS) is a representative ID in SGA-SS and has heterogenous (epi)genetic causes. The majority of variants are missense and difficult to interpret. Introduction: With development of high-throughput sequencing, diagnostic yield in congenital malformations (CM) and/or intellectual disability (ID) has increased rapidly as has the share of ultra-rare diseases (URD: prevalenceG). To identify the underlying causal variants, we subjected DNA samples of affected members of each family to whole-exome sequencing. Kucuksezer: None. Trifonova: None. Conclusions: Our systems analysis recapitulates hallmarks of OA and offers new insights into the modular structure of the protein interactome that is associated with OA chondrocyte biology. Abstracts from the 54th European Society of Human Genetics (ESHG) Conference: e-Posters Sponsorship: Publication of this supplement was sponsored by the European Society of Human Genetics. Seitz: None. Previously, a chromosomal translocation in two infertile brothers with breakpoints close to TEX13B was described and a recent publication reported a stop-gain variant in TEX13B as cause for azoospermia in one man. Materials and methods: The sequencing data from clinical exome sequencing of 100 Bulgarians, mostly under the age of 25 years, was analysed for rare/pathogenic genetic variants in 68 genes, known for its association with DM. The North of Scotland Genetics & Molecular Pathology Laboratory has offered fluorescent in situ hybridisation (FISH) testing on formalin fixed paraffin embedded (FFPE) RCC tumours for eight years. Demetriou: None. Kovtun: None. The reevaluation of previously collected data provides important evidence for assigning pathogenicity. Sajovic: None. van der Gaag1,5, Rick H. Dermitzakis1 1Department of Genetic Medecine and Development, University of Geneva, Geneva, Switzerland, 2School of Life Sciences, Ecole Polytechnique Federale de Lausanne (EPFL), Lausanne, Switzerland. Our study confirmed the importance of CNV analysis for the detection of new candidate disease-related genetic regions. Zaman: None. Each DNA sample was checked for concentration using a Qubit 3.0 Fluorometer. Aim of this study is to investigate the splicing consequence of a novel intronic mutation in SCN9A (NM_002977.3) in a case of congenital insensitivity to pain (CIP, #243000). Case report. Conclusions: We present the first familial case of IPPSD2 caused by a pathogenic synonymous-predicted variant in GNAS gene. For this purpose, we used GSE43591 dataset, which contains microarray profiling data obtained from 10 RRMS and 10 healthy individuals. Up until recently, the medical discipline of human genetics practically did not exist in Luxembourg and patients were mainly sent abroad. Golikova: None. Results: Most women ($n = 127$) were between 25-34 years old (60%), in a relationship (91%) and wanted to have children in the future (65%). Introduction: Multiple Sclerosis (MS) is a chronic neurodegenerative disorder resulting from an autoimmune reaction against myelin. Mikhailova2,1, Kristina Ushakova1, Alina G. P04.017.B Two novel variants in MMP13 gene in a Czech family with metaphyseal anadysplasia type 1 Lucie Hrušková 1, Helena Paszeková1, Ivo Mařík2,3, Veronika Krulišová1, Daniela Zemková4, Anna Vážná5, Zděnka Vlčková1, Renata Michalovská1 1GHC Genetics, s.r.o., Prague, Czech Republic, 2Ambulant Centre for Defects of Locomotor Apparatus, Prague, Czech Republic, 3Faculty of Health Care Studies, West Bohemia University, Pilsen, Czech Republic, 4Motol University Hospital, Prague, Czech Republic, 5Department of Anthropology and Human Genetics, Faculty of Science, Charles University, Prague, Czech Republic. Materials and Methods: We recruited 176 patients from 77 consanguineous families with NDDs with two or more affected individuals through clinical genetic and neuro-paediatric consultations from various academic hospitals in Turkey. Results: At the time of writing the collection of pipelines covers DNA, RNA and miRNA data analysis. C.S. Sabato: None. Conclusions: Homozygous normal embryos should be prioritized for transfer to exclude clinical phenotype that may ocur due to potential penetrance and expressivity differences. The estimated prevalence was calculated using the Hardy-Weinberg Equilibrium. Tolun: None. Introduction: In March 2020, COVID-19 pandemic (WHO) and state of alarm in Spain (Spanish government) were declared. P07.020.D Immunological profiling of patients with rare short stature, optic nerve atrophy, and Pelger-Huet anomaly (SOPH) syndrome Leonid Zhozhikov 1, Ayaan Ivanov1, Roza Ivanova1,2, Aitalina Sukhomyasova1,2, Filipp Vasilev1, Nadezda Maksimova1 1Laboratory of Molecular Medicine and Human Genetics, North-Eastern Federal University (NEFU), Yakutsk, Russian Federation, 2Republican Hospital #1, Yakutsk, Russian Federation. Macrocephaly, thick and dry hair, low anterior hairline, upslanting palpebral fissures, low set ears, high arched palate, pes cavus, ulnar deviation of 1st toes were notable findings along with mild intellectual disability. Mutations in TGFB3 are responsible for LDS 5, which is less symptomatic and without molecular analysis can easily be confused with MFS. Introduction: Exfoliation syndrome (XFS) is a systemic disease characterized by whitish fibrillar substance deposition in the anterior segment of the eye. Protein and mRNA expression level was measured using luciferase dual-assay and RT-PCR. Conclusions: Heterozygous pathogenic variants in SOX2 gene are associated with syndromic microphthalmia, including ocular and systemic abnormalities. Introduction: A disease association of biallelic variants in CCDC186, a downstream effector of RAB2 involved in dense core vesicle trafficking, has been previously suggested, but only a single patient has been described in the literature. Results: Serum immunoglobulins (IgA, IgM, IgG, IgE) were significantly reduced in SOPH patients in comparison with controls, CD4+ and CD8+ T cells amounts were unremarkable. Speakers Bureau/Honoraria (speakers bureau, symposia, and expert witness); Modest; BioMarin Pharmaceutical Inc, Sanofi-Genzyme, Takeda. Cheema10, M. Pathogenic variants in genes encoding these proteins can dramatically affect development and physiology. Editing efficiency was assessed by flow cytometry and TIDER. Affected cells might not survive in a homozygous deleted state, therefore prohibiting tumor development due to a large deletion affecting the wild type allele, a common somatic alteration in SMARCA4-related tumors. 3 of the Federal Law of July 5, 1996 № 86-FL"On State Regulation in the Field of Genetic Engineering" the regulatory legal framework for genetic engineering, including genome editing, genome diagnostics and gene therapy, is made up by federal (not International) laws and laws of the subjects of the Russian Federation. Ultimately, variants were considered pathogenic or likely pathogenic in 23 cases, with most phenotypes ranging from episodic or progressive ataxia to more complex ataxia syndromes, as well as with phenotypes dominated by non-cerebellar features such as intellectual disability and epilepsy. D.A. Wolf: None. SKAT-based testing resulted in 11 significant genes (FDR C has been demonstrated, while in the second family the c.655C>T heterzygous mutation has been identified, both without mutations in other LQTS genes. Carcajona: None. During pregnancy, structural ultrasounds were normal. The living child has hydroureteronephrosis, mildly impaired functioning of left kidney and preserved functioning of right kidney with non-obstructive clearance. Of these, the largest is an 81 Mb deletion in the long arm at Xq13.2q28 containing 370 OMIM genes and two deletions in the short arm at Xp22.2p22.11 and Xp11.3p11.23, 11.2Mb and 3.8Mb in size, containing 56 and 46 OMIM genes, respectively. No mutation was detected in one CSNB-patient suggesting the presence of another mutation segregating in the pedigree. Kassahn: None. Griffin: None. 11 Mb of target regions covering more than 4,900 genes, with known mendelian/inherited disease-causing mutations. In most cases, tumor cells contain a t(14;18) translocation that activates BCL2, a key gene for apoptosis. The most frequent mutations are the T408M($n = 12$) and E365K($n = 4$). For that purpose, instead of using all available knowledge and data sources, pilot applications may benefit from a reductionist approach. The same bone dysplasia occurs in the sister, mother, maternal aunt and maternal grandfather. Therefore, this study provide an overview of the clinical presentation and prevalence of lymphatic problems in patient with NS and Noonan-like syndromes. Hosmer-Lemeshow goodness-of-fit test and AUC were calculated to evaluate the accuracy and the predictive power of the models. Results: The cell viability is 50.1% for 22.5μM Ruxolitinib, 55.91% for 7.5μM MK-2206, 54.99% for 18μM Ruxolitinib+5μM MK-2206. P15.002.B The clinical utility of optical genome mapping for the assessment of genomic aberrations in acute lymphoblastic leukemia Jonathan Lukas Lühmann 1, Marie Stelter1, Marie Wolter1, Josephine Kater1, Jana Lentes1, Anke Katharina Bergmann1, Max Schieck1, Gudrun Göhring1, Anja Möricke2, Gunnar Cario2, Martin Schrappe2, Brigitte Schlegelberger1, Martin Stanulla3, Doris Steinemann1 1Department of Human Genetics, Hannover Medical School, Hannover, Germany, 2Department of Pediatrics I, ALL-BFM Study Group, Christian-Albrechts University Kiel and University Medical Center Schleswig-Holstein, Kiel, Germany, 3Pediatric Hematology and Oncology, Hannover Medical School, Hannover, Germany. This disorder is caused by biallelic mutations in the SLC7A7 gene. Consultant/Advisory Board; Modest; CSL Behring, Alnylam, Lupin. A.S. Shadrina: None. Beltcheva: None. Hernandez Dorronsor: None. The RPL3L gene should be routinely included in dilated cardiomyopathy genetic testing panels.Table 1. Bamshad: None. Struys: None. Introduction: Response to anti-TNF therapy is of pivotal importance in patients with Crohn's disease. Most represented pathways in terms of mutational frequencies are: PCP (32% of variants), folate metabolism (15%), embryonic development (11%), SHH pathway (8.4%), apoptosis genes (7%) and primary cilia (4.2%). Lejman: None. Plesa: None. Debniak: None. We observed more independent eQTLs per gene than per TEs in either state and a smaller distance of eQTLs to the TSS of TEs compared to genes (P T) in PIGV gene and an unknown, potentially pathogenic heterozygous variant (c.256 C>T) in PIGT gene. A patient showed two variants, one in CACNA1G, a gene related to Spinocerebellar ataxia with autosomal dominant inheritance, and the other one in KDM5B, a gene associated with autosomal recessive mental retardation. Kanabus: None. Introduction: Recurrent respiratory infections (RRI) in children represent a social issue. Ksiaa: None. Sánchez-Bolivar: None. P.A. Slominsky: None. The cytogenetic examination of an infant with pre and postnatal growth failure, normal psychomotor development, skeletal abnormalities and idiopathic hypercalciuria causing nephrocalcinosis, nephrolithiasis and brain calcifications, has incidentally identified an unexpected defect of chromatids cohesion during metaphase. Piñol: None. Wakeling, Rebecca Ward, Sarah E. D.S. Verbeek: None. Introduction: Inherited retinal dystrophies (IRD) are a heterogeneous group of diseases that mainly affect the retina, with more than 250 genes involved. Sequencing of probe area showed unknown variant rs897543876 (NM_001202.6:c.-144C>T). Heilmann-Heimbach: None. In order to control and reduce the prevalence of these infection within healthcare settings. Introduction: Luscan-Lumish syndrome is a rare disorder characterized by macrocephaly, intellectual disability, speech delay, low sociability and behavioral problems. Brösse: None. Lingenhel: None. Conclusions: This underestimated finding should not be overlooked in the molecular diagnosis of MFS patients and warrants an adaptation of the parameters used in bioinformatics analyses. Barbaux: None. Conclusions: Using an ES approach in a large cohort of patients with syndromic OC we identified molecular pathways and several new genes that are not traditionally known to be associated with clefting. Materials and methods: Analysis of the region 3´UTR LDLR of patients remitted to our center was performed by NGS using a customized panel of 198 genes. Results: 40 women aged 66.1+ 5.1 years (mean+standard deviation) and 31 men aged 68.1+6.5 were identified. Aguilera-Rodríguez: None. MLPA and WES led to the characterization of an additional ~37% of cases. Ceylaner: None. This variant also associates with HbF levels, although not significantly. While kataegis predominantly results from the activity of the APOBEC3B paralog, omikli results from the APOBEC3A paralog. In total, 118 samples (73 tumor and 45 normal DNA) from 49 patients were analyzed. Further rare causes (such as CTX, APTX, CACNA1A etc.) were detected in single families. Müller-Felber: None. Causative duplication includes two genes; BTRC is involved in Wnt signalling cascade by regulating β-catenin levels in limb development and POLL in base excision repair. Funding: Fundació La Marató (Proj.201726) E. Gasperikova: None. The aim: To analyze dynamics of T21 prevalence in the Moscow region - one of the largest regions of the Russian Federation for the period from 2011 to 2019. Materials and Methods: We used published data3 to partition SNP heritability. P06.027.D Novel missense variant in the INSR gene in Russian patient with metabolic condition: correction of the diagnosis Natalya V. Among pregnancies with sex chromosome abnormalities, 83,33% were terminated, including all of the cases with 47,XXY and half of the cases with 47,XXX karyotype. RRI are mainly caused by viruses, however, their course is often complicated by Staphylococcus aureus infections. García Santiago1, Elena Vallespín1,4, Ángela Del Pozo1,5, Mario Solís-López1, Angel Campos-Barros1,4 1INGEMM, IdiPAZ, Hospital Universitario La Paz, Madrid, Spain, 2Centro de Salud Galapagar, Galapagar, Madrid, Spain, 3Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain, 4CIBER de Enfermedades Raras (U753), ISCIII, Madrid, Spain, 5CIBER de Enfermedades Raras (U753), Madrid, Spain. Employment (full or part-time); Significant; GHOL, Groupement Hospitalier de l'Ouest Lémanique. Popp: B. Vicidomini: None. Next-Generation-Sequencing of a custom cancer panel with more than 700 genes including 41 CPS-related genes (SureSelect XT; Agilent, Germany) was analyzed using an in-house bioinformatics pipeline (megSAP). Among them, Duplex Sequencing (DS) has been shown to be highly-effective by leveraging the sequence complementarity of the two DNA strands. Preserved photoreceptors were seen above preserved RPE on OCT in Group 1. Our results confirmed that the AAGGG biallelic expansion is very common in patients with complete CANVAS (80%), but less common in the group with incomplete CANVAS (26.7%), consistent with previous studies. We report results obtained in Italy regarding trust in a set of selected social entities and willingness to share medical and DNA information (WTS) to these actors.We obtained responses from 1229 persons and performed multivariate correlation to analyse, among others i) trust as distributed per age ii) geographical distribution of WTS and differences amongst the different potential recipients of sharing iii) trust and WTS as related to religiosity. Maksimova1, Aiaan V. Ciaccio: None. Latorre-Pellicer: None. de Vries2, Trijnie Djikhuizen1, Yvonne J. Bagherjad Salehi: None. L.V. Roshcheniuk: None. All patients presented a significant improvement of their auditory skills in subsequent intervals at 5th (p 30% (M368V, A122V) residual HGD activity. Yamamoto: None. Zschocke: None. Molecular endophenotypes such as miRNA expression levels, which are more specific and closer to the genomic effects, might facilitate the identification of genetic determinants. To study how this mutation alters receptor expression and biophysical properties we combined patch-clamp recordings, BRET experiments and immunocytochemistry, using HEK cells expressing wild type or mutated NMDA receptors subunits or patient fibroblasts reprogrammed into induced pluripotent stem cells (iPSCs) and differentiated into neurons. Koolen: None. Karyotype showed mosaic presentation of 46,XY,der(7)(p+) in 10% of the cells. Slob: None. P18.036.B Understanding of pharmacogenomic testing, adverse drug reactions, and implementation barriersBernard Esquivel, Ghada Elnashar, Ellie Jhun, Jessica Savieo, Elimear O'Mahony, Victor Tam, Kurt Wiersma, Julie England OneOme, Minneapolis, MN, USA. (2019): (1) a fluorescently labelled PCR was used to amplify the repeat's region; (2) three specific repeat-primed PCRs (RP-PCRs) were performed, each targeting one of the known pentanucleotides - presence of the continuous stutter peak profile in the AAGGG-specific RP-PCR, and absence of similar results in the other two PCRs, is compatible with the diagnosis of CANVAS. Oosterloo2, Maxim B. Miedema2, Harro Seelaar1, Netherlands Brain Bank3, August B. Amplicons were captured by a custom Sure-Select kit (Agilent) and sequenced on HiSeq (Illumina). 54% received cochlear implant rehabilitation, 16% of which were bilateral. In our cohort we evaluated the usefulness of exome sequencing (WES) in identifying the genetic etiology for pregnancy loss. Vogrinc: None. Conclusion: We conclude that CNA-associated chromosomal breaks within genes represent a highly prevalent and clinically relevant subset of somatic variants (SVs) in HNSCC. P01.052.D Locus-specific methylation of the ESR1 gene promoter region as a marker for the prognosis of placental insufficiency and perinatal loss Zoia I. Schubert: None. Five patients developed cancer (1.9%): nephroblastoma at age 9; granulosa juvenile tumor at age 16; gastric adenocarcinoma at age 52 ; myelodysplasic syndrome at 55 and basocellular carcinoma at 59 in the same patient; clear cell renal carcinoma at age 38. Resbeut: None. These results provide an accurately analysed and interpreted set of variants to be taken into account by clinicians and the scientific community, and hence, aid the precise genetic counseling to patients. D.N. Nikolova: None. Conclusions - The results of this study improve our understanding of the relationship between chronic, subclinical infections and human health. A 5 days old full term baby girl was admitted to our pediatric intensive care unit with non ketotic hypoglycemia, abnormal movement along with bradycardia and progressive prolongation of the QT interval. Potočnik: None. Excitingly, these deficits could be largely rescued by the addition of recombinant CRISPs to sperm. Segregation was investigated by FISH. Further optimization of the delivery protocols for plasmids and RNP increased the efficiency of mutation correction in EGFP to 16.99% (p T, p-value = 4.1e-9, beta = -2.4 years). Mancini1, Kevin C. Mauri: None. Auranen: None. Whole exome sequencing analysis was performed from the patient who had ichthyosis and frequent infections.ERCC2:c.2164C>T and ERCC2:c.1867dup heterozygous mutations were detected. Gait and limb ataxia, mild cognitive impairment occured in adulthood. Lanfrancone: None. Vento Torres: None. Results: Next-generation sequencing of the gene panel was successful and identified 24 variants in 20 probands for further analysis. Laurikka: None. Potocki: None. Investigation of pedigrees found other cancers reported in families with RAD51C/D mutation carriers, with colorectal, lung, prostate, pancreatic cancer and leukemia being the most prevalent ones among first relatives. The phenotype scores were highly variable from abnormal skin pigmentation only to one or more extracutaneous features, even though there was no meaningful significant difference for each clinical characteristic between the groups with sequence variants and common large deletion. RNA-seq has gained more visibility by holding the promise to improve the diagnostic yield in unresolved cases of rare Mendelian diseases. Lucassen: None. The biobank facilitates the management of such a collection making it technically and ethically suitable for research. Objective: It has previously been shown that pathogenic variants in the GABRB3 gene increase seizure susceptibility and lead to a broad phenotypic spectrum ranging from severe developmental and epileptic encephalopathies to milder epilepsy syndromes such as generalized epilepsy with febrile seizures + and childhood absence epilepsy. J.A. Ruskey: None. A c.34G>C (rs750597721) mutation in GATA4 gene was identified and confirmed as pathogenic using bioinformatic tools. Makarova: None. MobiDetails is totally free for use to academics and does not require any account to annotate a new variant and browse the results. Hemizygous pathogenic variants in the underlying X-chromosomal NONO gene were confirmed to cause a rare syndromic disorder. Besides, its association with epithelial to mesenchymal transition requires better comprehension. Bouyakoub: None. The main features of patients with an 8q21.11 deletion encompassing this gene are intellectual disability, hypotonia, short stature, and a peculiar facial phenotype. Adv. Results: We identified a novel frameshift variant; c.605-606insA (p.H202Qfs*265) at a heterozygous state in exon 5 of the STK11 gene for the 2 patients. Fuster-Tormo: None. Introduction: Hypertrophic cardiomyopathy (HCM) and idiopathic dilated cardiomyopathy (DCM) are the most common referral in Inherited Cardiovascular Condition (ICC) Genetics Service. Results: RT-PCR of mRNA from PPCs from a patient carrying c.4539+1G>T and c.5714+5G>A using primers in exons 38 and 44 showed a major normal product and minor exon 40 and exon 39/40 deletion products. Our murine model with physiologic levels of Ifitm5 S42L expression recapitulates patient phenotype and will be used to investigate mechanisms and pathways involving Ifitm5 and Serpinf1. Pauta: None. This project aims to improve variant classification by the development of APC-specific classification criteria within the approval process of a Hereditary Colon Cancer / Polyposis Variant Curation Expert Panel (VCEP) from the International Society for Gastrointestinal Hereditary Tumours (InSiGHT) and ClinGen. García Vázquez: None. Pozo-Román: None. van Zelst-Stams1 1Department of Human Genetics, Radboud University Medical Center, Nijmegen, Netherlands, 2Department of Health Sciences and Primary Care, University Medical Center, Utrecht, Netherlands, 3Department of Neonatology, Radboud University Medical Center, Amalia Children's Hospital, Nijmegen, Netherlands. 2018-01 to VT and grant RF-2018-12366703 to VC, VB and VT. The VWF gene was sequenced by the next generation sequence analysis method. Other findings reported are cardiac anomalies, thumb anomalies, esophageal atresia, short stature, spine anomalies. Hospital Universitario La Paz, IdiPAZ, Madrid, Spain, 7Preanalytic Section. It substantially limits the applicability of this approach for the analysis of samples with restricted target DNA amounts. PGs are important for the constitution and functioning of the connective tissue. Conclusions: Our cases expand the known phenotypic range for rare genes causative for HON plus. Joensuu: None. This insertion possibly leads to a gain-of-function effect. Two patients had atypical PD with spasticity and/or pyramidal signs. P.P. Khincha: None. P24.036.C Host genome variants influence on bacterial salivary composition in African admixed populationAntonio Espuela-Ortiz1, Esther Herrera-Luis1, Fabian Lorenzo-Diaz 1,2, Celeste Eng3, Scott Huntsman3, Michael A. In addition, the high concordance ($R2=0.95$) of population allele frequency for 43 common SNPs in the control European population (gnomAD) and our experiment confirmed the reliability of pooled sequencing. Ordinary paediatrician was not able to order the genetic test for KMS easily until 2020. As iris coloboma is the only consistent phenotype, these data highlight the importance of additional pathogenic variants underlying associated complex non-ocular phenotypes. A.I. Esterhuizen: None. Pathway analysis confirmed the involvement of sensory perception of sound, actin-binding, and filament polymerization in ARHL. Exome sequencing (ES) was performed using a parent-offspring trio approach. Escande: None. Results: Trio whole-exome-sequencing was performed in the mother and her unaffected parents without conclusive results. He: None. Our study suggests that a collaborative approach to developing a European assessment would help standardise training requirements, assisting mobility of specialists across Europe. The mutations spanned almost the entire coding region of the GLI3 gene (c.366 - c.4172) and were mostly amorphic. Nature of the relationship was determined by CompuSyn software. X.S. Yin: None. Reusink: None. DNA samples were analyzed on Ion Torrent platform, using an AmpliSeq AIS gene panel, which included 34 genes (ASAH1, CARD14, DDX58, ELANE, IFIH1, IL10RA, IL10RB, IL1RN, IL36RN, LPIN2, MEFV, NLRC4, NLRP12, NLRP3, NOD2, MVK, PLCG2, PSMB8, SAMHD1, RBCK1, SLC29A3, RNASEH2B, ADAR, RNASEH2A, RNASEH2C, TNFAIP3, TNFRSF11A, TNFRSF1A, NLRP1, OTULIN, TMEM173, HAX1, PSTPIP1, TREX1). Moreover, the structure of sessions should be tailored to the specific requirements of remote counseling and suitable training efforts should be promoted to enhance professionals' communication skills in such setting. An autosomal dominant; heterozygous mutation in the TPM1 gene (α-tropomyosin), NM_001018005.2:c.203A>G, p.Gln68Arg, was identified and validated by Sanger sequencing in all affected members of the family but was absent in the unaffected family member. Variant prioritization was based on sequence quality assessment (Q>30); coverage (mean >90x; %bp>20x >80%); population frequency (MAF 20). Starzynska: None. Methods: We investigated somatic mutations of 25 epigenetic regulation genes, using the NGS panel in 95 GC samples. P09.138.C Bi-allelic variants in HOPS subunit VPS41 cause cerebellar ataxia and point to differential lysosomal dysregulation in brain cell types Leslie E. Valieva1, Anna E. Materials and methods: The patient had atypical clinical symptoms since childhood (chronic sinusitis mostly, polypotomy at the age of 17). The participants were recruited from two Saudi Arabian cardio-genetic centres and investigated via interpretative phenomenological analysis. Tikhonov1, Vladimir A. The aim of this study was to screen uterine lavage fluid and tissue samples from Lithuanian OC and EC patients for mutations related to gynecological cancer and to determine their associations with clinical features. We also performed WGS on two trios with rare diseases who were WES-negative. Bartosch: None. Fisher's exact test was used for comparison of allele frequencies. Interestingly, there is one case published, with mild clinical features and no limb reduction abnormalities (Gogh et al., 2010). The presence of MMR-deficient glands correlated with the hs-MSI levels. Cuna: None. Data underwent standard quality control. Results: Identification of disease-causing mutations was achieved in 42% of studied families (25/59) who could receive a genetic diagnosis and counselling. Cesario: None. Günthner: None. Adam: None. Conclusions: Mitochondrial disorders may be caused by pathogenic variants of genes encoded by either nDNA or mtDNA, thus combining a high-quality mtDNA analysis with routine panel-based diagnostics improves the diagnostic yield. Two PADI6 variants, p.Leu555Profs5ter and p.Asp547Asn, were detected in case 1: she had a reproductive history countersigned by nine miscarriages and a unique born child with BWS-MLID. P01.094.B Mosaicism for genome-wide paternal uniparental disomy - two prenatal casesRaquel Lemos1, Cíntia Ventura1, Fátima Torres1, Gabriela Fernandes1, Isabel Durães1, Áurea Pereira1, Patricia Costa1, Jorge Castro2, Conceição Brito2, Rita Cerqueira 1 1CGCgenetics UNILABS, Porto, Portugal, 2CHVNG, Obstetrícia, Vila Nova de Gaia, Portugal. Introduction: Research shows that lifestyle influences the human epigenome by altering DNA methylation patterns. of Neurosciences, Unit of Neurology, Padua, Italy. The most common brain malformations are corpus callosum abnormalities, periventricular nodular heterotopia, polymicrogyria, hydrocephalus, ventriculomegaly and cerebellar malformations. Alvarez-Sanchez: None. Introduction: Pathogenic and likely pathogenic HACE1 variants are associated with spastic paraplegia and psychomotor retardation with/without seizures (SPPRS), a rare autosomal recessive, progressive neurodevelopmental disorder characterised by hypotonia, weakness and spasticity of the lower limbs, and seizures. Ophthalmologic examination was completely normal. Introduction: Duchenne muscular dystrophy (DMD) is an X-linked disease due to pathogenic variants in the DMD gene. Conclusions: We provide evidence for 3 loci that modulate plaque composition through macrophages and smooth muscle cell plaque proliferation and cell-cell interactions. A.A.K. Sreelatha: None. The MMIC is a compound assessment tool with three elements: relevant knowledge; outcome value, and test decision. Due to the KS patients having an extra X-chromosome it might be explained with a similar mechanism. While advances in next generation sequencing (NGS) have provided a standardized way for accurate coding variant analyses through whole exome sequencing (WES), CNV detection still relies on probe-based methods, that are complementary to NGS approaches in clinical diagnostics. 199300) is an autosomal dominant familial cancer syndrome with the estimated incidence 3/100 000. Discussion: Our preliminary results suggest that a portion of genetic testing can cost-effectively be performed by array-based genotyping. Consultant/Advisory Board; Modest; Novartis, Sanofi Genzyme, Almirall, Merck-Serono. Aleksiuniene: None. Koroleva, Elena Yu Bragina, Aleksei A. Ha-Vinh Leuchter: None. Our aim was thus to evaluate miRNAs enriched in serum EVs as potential prognostic biomarkers in MM patients. Objectives. Vandromme: None. Four variants in the KMT2D gene (p.Cys1534Ter, p.Leu3542ValfsTer13, p.Gln4412Ter and p.Glu4422Ter) were novel. O'Connell: None. Kedar: None. Results: Pathogenic variants and variants of uncertain clinical significance were identified in a number of the CRC associated genes in the patients. Materials and Methods: We looked into the medical record of 5 patients diagnosed as KMS since 2013 till now retrospectively. Four mutations were identified in the two major HCM genes: missense changes p. Introduction: The findings about the role of Homologous Recombination Repair (HRR) genes in Prostate Cancer (PC) risk, lead to the inclusion of a target genetic testing into the last clinical practice guidelines. No false positives were detected. The majority of these findings belong to the phenotypic spectrum of SGBS1 with the exception of intrauterine growth retardation. We explored many plausible links between childhood adiposity and breast cancer risk, but none of the reviewed traits in this work accounted for the protective effect observed. The prenatal diagnosis led to TOP in 12 cases (34%), in a mean stage of 32 weeks. Currently, among the population of Yakutia, the accumulation and spread of the SCA1 mutation continues. Materials and Methods: We cumulated mtDNA variants reported as variants of uncertain significance in routine diagnostic exome sequencing and targeted mtDNA next generation sequencing. Bruckner: None. STAG1 gene variants (OMIM: Mental retardation, autosomal dominant 47, #617635) belong to a group of cohesinopathies and are previously described only in few cases, as a cause of unspecific intellectual disability. In parallel, we overexpressed AGO1 mutant proteins in neuronal (Neuro2A) and non-neuronal (HeLa, HEK293) cells. Since its first description in 1998, only 12 individuals from 7 families have been reported, carrying homozygous or compound heterozygous frameshift or nonsense variants in YY1AP1. Verhoeven: None. Results: We identified two heterozygous pathogenic variants in the TH gene: c.605G>A(p.Arg202His) and c.614T>C(p.Leu205Pro), associated with an autosomal recessive form of L-DOPA-responsive infantile Parkinsonism. We conclude that dysregulation of receptor trafficking and cell adhesion are relevant in the pathobiology of CS. On the other hand, no correlation between PFS and somatic variants, age at diagnosis, CCRCC grading, or lymphovascular invasion was found. The broad and variable spectrum of clinical manifestations includes global developmental delay, autistic features and neuropsychiatric or behavioral issues, seizures and distinct dysmorphic facial features. We observed that combined treatment activates PTEN and P53, decreases PI3K expression in MDA-MB-231 cells. Férec: None. Khrapko: None. Bachetti: None. gingivalis significantly decreased the expression biomarkers associated with antiapoptotic mechanisms in HCAECs, HASMSs, HUVECs. Conclusions: Data-analysis revealed the significant effect of some periodontopathogens on proatherogenic mechanisms. For hierarchical clustering we attempted to identify the most differentially expressed genes in both batches of samples. Dekker: None. Recently, four different biallelic pathogenic variants in Mesoderm Development LRP Chaperone (MESD) were shown to cause a progressively deforming recessive type of OI, associated with recurrent fractures and oligodontia in five patients of five families. Turner, David Stoddart, Sissel Juul, Eoghan Harrington, Philipp Rescheneder Oxford Nanopore Technologies Ltd, Oxford, United Kingdom. We show that SCUBE3 is an auxiliary protein that acts as a BMP2/BMP4 co-receptor, recruits the BMP receptor complexes into raft microdomains, and positively modulates signaling possibly by augmenting the specific interactions between BMPs and BMP type I receptors. Geromel: A. Results: All 321 newborns carried at least one variant at the five DPGW recommended PGx genes. Sudlow: None. Further findings were right hydrocele testis, and a small sacral dimple. P.W. Whitworth: B. Patient Methods P1;Mother Sequencing c.246C>T (hemizygote;heterozygote) P2 SNP-Array 2.26Mb deletion P3 WES c.1867delC Here, we report five affected males and a manifesting female from three unrelated families. Peeters-Scholte13, Hamid Galehdari14, Neda Mazaheri14, Genomics England Research Consortium, Sanjay M. Introduction: Schizophrenia is a disabling neuropsychiatric disorder of adulthood onset with high heritability. Mall: None. Ivaschenko: None. Main findings: heart defects (76%), short stature (53%), microcephaly (40%) and intellectual disability (ID) (35%). Patiño-García: None. It explains the phenotype of our patient likely by causing nonsense mediated decay resulting in the non-functional ECM1 protein. Pospíšilová: None. A targeted NGS panel was designed to sequence 150 skeletal dysplasia genes. Molecular elucidation is important for the assessment of therapeutic options for these patients. The most frequent somatic mutation in DNMT3A is R882H (c.2645G>A); this amino acid substitution reduces the enzymatic activity of the protein and destabilizes its functional tetrameric form in vitro and in vivo. Results: TSC1/TSC2 mutations were identified in 27 of 30 patients (90%) [21(78%) in TSC2; 6(22%) in TSC1]; 25 patients had mosaicism [blood VAF:0-19%, median:2.8%]. The accumulation of the mutation continues in the Central focus. J.G. Gleeson: None. Hunter syndrome a genetically associated to the deficiency of the iduronate 2-sulfatase enzyme (IDS). C. Other characteristic features of this condition are macrocephaly, visual impairment, splenomegaly, and bone marrow failure. M.J. Daly: None. The effect of this deletion on RNA and protein expression levels, was also determined by in vitro assays, and compared to two TFAP2B missense variants (c.C706T and c.C898T) found in patients with Char syndrome. In silico splicing prediction algorithms were in favor of a deleterious effect of this variant, by creating a new donor splicing site. N.L. Gentle: None. The E255K/V mutation was detected in a male who died shortly after inclusion in this study. Kuismin: None. Results: All affected individuals shared a homozygous block including PRKN. Altiner: None. Vozzi: None. Employment (full or part-time); Significant; Invitae Corp.. For this reason, we analyzed exome sequencing data of 4.329 patients consecutively referred to our center for diagnostics of diverse rare genetic disorders. Park: None. Lançon: None. Conclusions: In the case of patients with intellectual disability and autism spectrum disorders, BRPS should be considered in the differential diagnosis. P17.063.B Phenotype-Tissue Expression and Exploration (PTEE) facilitates RNA-seq-based Mendelian disease diagnosis Akhil Velluva 1,2, Maximillian Radtke3, Susanne Horn2, Konrad Pltazer3, Erind Gjermeni4, Johannes R. Each individual carried in average 2.2 alleles and 93% of the cohort could be informed of at least one actionable pharmacogenetic phenotype. Parker: None. Various molecular bases underlying primary PIPO have been identified, of which ACTG2-related visceral myopathy is the most common for familial or sporadic (de novo) primary PIPO with autosomal dominant inheritance. Genetic testing reported two variants in exon 8 of FH gene. P11.009.C AKT3 variant in a patient with macrocephaly Florina Victoria Nazarie 1, Simona Bucerzan1,2, Monica Mager3,2, Diana Miclea1,2 1Genetic Department, Emergency Hospital for Children, Cluj-Napoca, Romania, 2Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania, 3Pediatric Neurology Department,Emergency Hospital for Children, Cluj-Napoca, Romania. We have recorded variants of unknown clinical significance among 25 % of patients. Nanda: None. Materials and Methods: The study group included 165 BC patients with a follow-up period of 28-36 months. Takroni: None. Zdraveska: None. Among these were 119 structurally normal fetuses. Bartoli: None. Adam, H. Juntas Morales: None. Quinodoz: None. P09.058.C Characterization of SUMO2/3 protein levels in Fragile X-associated tremor/ataxia syndrome patients Laia Rodriguez-Revenga 1,2, Tamara Barcos1, Emma Peruga1, Laura Molina-Porcel3,4, Maribel Alvarez-Mora1,2 1Hospital Cinic, Barcelona, Spain, 2CIBER of Rare Diseases, Instiuto de Salud Carlos III, Barcelona, Spain, 3Alzheimer's disease and other cognitive disorders unit. His idea was, to subsume under such a term all chromosome-related research with the goal to lead us to novel concepts in biology. Rodriguez-Sodupe: A. Cogo: None. Alders2, A Dingemans3, E Gerkes4, B.W. van Bon5, J.C. Dempsey6, D Doherty6,7, I Miller8, J.A. Rosenfeld9,10, S Moortgat11, K Parbhoo12, M Pastore12, D Regier8, B Schmalz12, T Smol13, K.E. Stuurman14, B.B.A. de Vries3, S.E. Hickey12,15, I Maystadt*11, G.W.E. Santen*1 1Department of Clinical Genetics, Leiden University Medical Center, Leiden, Netherlands, 2Amsterdam UMC, University of Amsterdam, Department of Clinical Genetics, Amsterdam, Netherlands, 3Department of Human Genetics, Donders Institute for Brain, Cognition and Behaviour, Radboud university medical center, Nijmegen, Netherlands, 4Department of Genetics, University of Groningen, University Medical Center Groningen, Groningen, Netherlands, 5Department of Human Genetics, Radboud University Medical Center, Nijmegen, Netherlands, 6Department of Pediatrics, University of Washington, Seattle, WA, USA, 7Center for Integrative Brain Research, Seattle Children's Research Institute, Seattle, WA, USA, 8Genetics and Metabolism, Children's National Hospital, Washington, WA, USA, 9Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA, 10Baylor Genetics Laboratories, Houston, TX, USA, 11Centre de Génétique Humaine, Institut de Pathologie et de Génétique, Gosselies, Belgium, 12Division of Genetic & Genomic Medicine, Nationwide Children's Hospital, Columbus, OH, USA, 13Service de génétique clinique Guy Fontaine, CHRU de Lille-Hôpital Jeanne de Flandre, Lille, France, 14Erasmus MC, University Medical Center Rotterdam, Department of Clinical Genetics, Rotterdam, Netherlands, 15Department of Pediatrics, The Ohio State University College of Medicine, Columbus, OH, USA. Loss of function GJB2 mutations are related with nonsyndromic deafness. Zarubin: None. Chromosome 13q deletion syndrome is a rare chromosomal disorder. Karyotype of a child 46,XX. Future efforts will further evaluate statistical considerations of complementary polygenic approaches to traditional TWAS. The T315I mutation is key mutation with relevant clinical implications - can only be overcome by third generation tyrosine kinase inhibitors. Devasia: None. Lysosomal storage are incriminated in up to 29.6% of NIHF cases.We report the history of a family with recurrent hydrops fetalis revealing a mucopolysaccharidosis type VII (MPS VII). The top hit is an intronic variant of genes AAMDC and INTS4 found to be a blood expression quantitative trait locus for INTS4 ($p\text{-value} = 1x10\text{-}8$), AAMDC ($p\text{-value} = 8x10\text{-}24$), and AQP11 ($p\text{-value} = 5x10\text{-}14$), the latter being potentially involved in saliva volume regulation. Biallelic SYNE1 mutations are known to cause autosomal recessive spinocerebellar ataxia-8 (SCAR8), which is a slowly progressive neurodegenerative disorder characterized by gait ataxia with cerebellar signs, such as nystagmus and dysarthria. Only 1 of these 14 patients developed metastases. Further investigations into their roles in MS pathogenesis and progression are merited.This work was funded by KFAS grant 2012-1302-02. M.H.G. Monje: None. Methods: Our patient underwent a series of clinical and neuroimaging examinations at two time points (2011 and 2017). F.A. García Santiago: None. Discussion: In the present work, we propose to report an association of the synonymous variant p.49Glu = in exon 2 to the pathogenic variant p.Arg138* at exon 4, both at the PMVK gene. Pinese: None. The effect of compound heterozygosity with another frequent KIV-2 splicing mutation (4925G>A) was assessed. Carneiro: None. Iascone: None. Pulverer: None. P14.025.B A novel case of a girl with partial trisomy 12q24.21q24.33 and review of the literature Lautaro Plaza-Benhumea 1, Monica Martin-DeSaro2, Olga Messina-Baas3, Sergio Cuevas-Covarrubias4 1Hospital Perinatal, Monica Pretelini, EdoMex, Mexico, 2Pediatrics Department, Hospital Materno Infantil ISSEMyM, EdoMex, Mexico, 3Hospital General de Mexico, CDMX, Mexico, 4Hospital General de Mexico, Universidad Nacional Autonoma de Mexico, CDMX, Mexico. Selloum: None. Results: Both patients show the main clinical features of the disorder.The younger patient presented normal enzyme activity, a heterozygous pathogenic variant and also a heterozygous variant of uncertain significance, identified in the MAN2B1gene, associating a high level of urinary secretion of mannose -rich oligosaccharides. Materials and Methods: Genotypic, demographic and lifestyle data on 235 PD-patients and 464 healthy controls were obtained from a case-control study previously carried out in the Cypriot population. DNA was extracted from peripheral blood from all 50 patients. Rietveld: None. Recent studies suggested the STAP1 (signal transducing adaptor family member 1, OMIM#604298) as fourth FH gene2. P11.073.C Two novel presentations of KCNMA1-Related Pathology - Expanding the Clinical Phenotype of a Rare Channelopathy Jotte Rodrigues Bento 1, Candice Feben2, Marlies Kempers3, Maartje Van Rij3,4, Mallory Woiski4, Koenraad Devriendt5, Luc De Catte6, Marcella Baldewijns6, Josephina Meester1, Aline Verstraeten1, Willy Hendson7, Bart Loeys1,3 1Centre of Medical Genetics, Antwerp University Hospital/University of Antwerp, Antwerp, Belgium, 2Division of Human Genetics, National Health Laboratory Service & The School of Pathology, University of the Witwatersrand, Johannesburg, South Africa, 3Department of Human Genetics, Radboud University Medical Center, Nijmegen, Netherlands, 4Department of Gynaecology and Obstetrics, Radboud University Medical Center, Nijmegen, Netherlands, 5Department of Human Genetics, Catholic University of Leuven, Leuven, Belgium, 6Department of Gynaecology and Obstetrics, Catholic University of Leuven, Leuven, Belgium, 7Department of Paediatrics, Rahima Moosa Mother and Child Hospital & The University of the Witwatersrand, Johannesburg, South Africa. Tichy: None. Wet tested the ability of molecular methods to identify E255K/V and T315I mutations in BCR-ABL gene. In this study, the validation data of 64 patients with carrier screening panel targeting coding regions of 420 genes are presented. For this purpose we treated the fibroblasts with triamterene alone (90 μM) and triamterene in combination with different concentrations of (21, 62, 125, 250, 500, 1000 μg/ml) valproic acid (VPA), which is a HDAC inhibitor. Accurate diagnosis of lysosomal storage disorders like MPS VII is essential to give the family an adequate genetic counselling. Özbek: None. We studied 45 cases of this cohort and genetic diagnosis was reached in 71% of newborns. Conclusions: Evidence for a sex-specific effect of SNP rs7969300 on the age of onset of SCA2 patients is provided. Gene panel and whole exome sequencing is now mainstream in clinical practice. Młynek: None. Chromosomal microarray revealed the familial 0,1Mb deletion on 2p16.3 involving MSH6 and trio-WES was without pathogenic variants. Conclusions: Dissection of T2D risk variants into distinct pathways improved our ability to detect causal relationships between specific T2D pathways and cancers and highlighted hormonal-lipid- and glycaemia-related mechanisms underlying these relationships.Funding: WCRF-2017/1641, LongITools H2020-SC1-2019-874739 Z. Evaluation of genetic cause is often challenging, and many patients undergo a "diagnostic odyssey". Taylor 1,2, Jeffrey M. No somatic variants were identified in gynecological samples from controls or blood from any women. Duriez: None. Ongen: None. J.W. Zyskind: None. The pathophysiological mechanisms are still unknown. Fetal and maternal insulin resistance have been linked to differences in birth weight. Materials and Methods: We applied logistic regression to estimate the association of PRS-313 with breast cancer risk using 3,925 breast cancer cases from 3,528 non-BRCA1/2 breast cancer families and 3,479 population controls. Other 41(12%) children were clinically diagnosed based on specific phenotype. We suggest ITSN1 gene is involved in development of an autism spectrum disorder with variable additional neurodevelopmental deficiency, thus confirming the hypothesis that ITSN1 is important for brain development. Inclusion of the daughter led to the identification of a previously reported likely pathogenic variant in the SAMD9L gene (NM_1512703.4:c.2956C>T; p.(Arg986Cys)). Freeman, Bernadette R. Other abnormalities were: mild intellectual disability, epilepsy, walking difficulty, leg bone pain, genu varrum, pes planus, and patent foramen ovale. Gort: None. Watrin: None. To determine the effect of identified splice site variant on mRNA structure, total blood mRNA of the proband was isolated, template cDNA was synthesized, and Sanger sequencing was performed. Torrente: None. Heterozygous pathogenetic variants in POGZ gene have been associated to a syndromic NDD, including autism spectrum disorder (ASD), developmental delay (DD), intellectual disability (ID) and some dysmorphic facial features. This can create dilemmas for health care providers around what should be the scope of PGT. We hypothesize that via its direct effects on the efficiency of viral egress, it may serve as a potent therapeutic decreasing the replication and infectivity of the virus. T.R. de Back: None. Armengol: A. Gene-SCOUT (Gene-Similarity from COntinUous Traits) is a gene similarity score that takes a user-defined gene and identifies other human genes with a similar quantitative trait fingerprint. Dommering2, Mirjam M. Chukhrova: None. The proportion of people with higher education is high (46%), 61% of participants played sports for a long time, and 70% never smoked. We aimed to identify additional inherited risk factors by performing exome sequencing in 44 non-related SP cases followed by a pathway-centered analysis. Stepanov: None. We examined that localization of PAD4 and PAD2 protein was indicated by immunohistochemistry in CIA mice. Results: At time of acute illness, plasma clinical untargeted metabolomics from our patient showed significant alterations in nicotinamide/NAD+ metabolism (z score negative 4-6), along with a footprint of peroxisomal-mitochondrial axis dysfunction: alterations of TCA cycle metabolites, branched chain amino acids (z score negative 2-3), plasmalogens, phospholipids, and lysophospholipids (z score negative 2-4). Her mother and maternal grandmother also appeared with the same condition with an onset during the second decade. Non-ocular symptoms include hearing loss, but also signs of connective tissue fragility, placing it in the Ehlers-Danlos syndrome (EDS) spectrum. P12.057.A Application of targeted next-generation sequencing in primary and metastatic colorectal cancer using hot-spot panel for detection of potentially therapeutically relevant rare variants Zora Lasabová 1, Peter Mikolajcik2, Dusan Loderer3, Marian Grendar3, Eva Gabonova2, Ivana Kasubova4, Tatiana Burjanivova1, Michal Kalman5, Lukas Plank6, Ludovit Laca2 1Comenius University in Bratislava, Jessenius Faculty of Medicine in Martin, Dept. Materials and methods: We have analyzed by cytogenetic analysis 1063 men, attending reproductive clinic. Results: The analysis of genotypic and allelic distribution of rs1048290 SNP in Keap1 gene and rs2706110 SNP in NRF2 gene did not show statistically significant differences between both groups of subjects. Deficiency of either NAXD or NAXE depletes the NAD+ pool and results in fever-triggered fatal encephalopathic crises (MIM 618321 and 617186, respectively). Geneviève: None. Boyle et al. Code Availability: R.S. Aldisi: None. SNP genotypes were used to detect the disease gene locus and to investigate for any deletion or duplication linked to the malformation. Analysis of the spatial distribution revealed linear clustering of these variants in the N- and C-terminal protein region, in line with higher restrain for missense variation as indicated by higher computational scores and depletion of homozygous missense variants. It is thought they play a role during the early stages of embryonic development. of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy, 6Child Neurology and Psychiatry Unit, IRCCS Mondino Foundation, Pavia, Italy. Breakpoint junction analysis and analysis of cDNA from patient fibroblasts allowed for characterization of the genomic rearrangement. Zobkova: None. Results: The web application successfully replicated the results from the previous cases. Early identification of the genetic cause favour the efficient management of these children, provide prognostic information and allow genetic counselling of families. Whole genome trio sequencing revealed a likely pathogenic missense variant in the ABCC9 gene (NM_005353286.2); c.1745T>A (p.Val582Asp), which the boy shares with seven similarly affected family members (patent ductus arteriosus, pericardial effusion, cardiomegaly, coarse facial features and hypertrichosis). Jarmalaite: None. P02.029.B Use of OTO-NGS-v2 panel for the genetic diagnosis of hereditary hearing loss María Lachgar 1,2, Matías Morín1, Manuela Villamar1, Miguel Ángel Moreno-Pelayo1 1Hospital Universitario Ramón y Cajal and IRYCIS and CIBERER, Madrid, Spain, 2Wolfson Centre for Age-Related Diseases, King's College London, London, United Kingdom. Most functionally active (rank = 1-2) remained the genes of the ubiquitin-ligase family and key processes belong to the pathways of interferon signaling (FDR = 0,004). We subsequently show that diagnostic WES on the top 10% of patients with the highest probability of a positive WES result would provide a diagnostic yield of 57%, leading to a notably 86% increase. Van Damme: None. Parini: None. In order to recommend routine screening for autoimmunity in asymptomatic patients, continuous monitoring will be required for possible emergence of autoimmune disease. The authors presented a rare duplication involving 8p11 region. the North Caucasus. Lantero: None. Hanna: None. D.J. Green: None. Conclusion: We were able to outline factors that impact on considerations of utility of

PGS use in healthcare. Forde: None. Second, we confirmed the monozygosity of patients 5& 6. Despite the accessibility of PCR/CE as an assay format, downstream analysis is tedious, manual, and error prone. Nestoroska: None. Further, association of ctDNA detection rates with tumor stages was shown, as 0/4 stage-I, 4/8 stage-II, 3/4 stage-III and 6/6 stage-IV patients were found ctDNA-positive. Funding: This work was funded by The Foundation of Aase and Ejnar Danielsen, The Foundation of 17-12-1981 and The Novo Nordisk Foundation. Cells were exposed to oleate (0-100μM) or BSA control for 24hrs, and neutral lipids were stained with Nile red, visualized by fluorescence microscopy, and quantified by FACS. Chudakov: None. The control samples had repeats below the pathogenic cutoff. 228,10 kb -0,964 Partial deletion of GJB6 and CRYL1 Ht AR Pathogenic AF fetus 13q12.11(20,798,175-20,803,032)x1 6,87 kb -1,403 GJB6 and CRYL1 Hm AR Pathogenic -6,477 -1,310 DFNB1 locus could present two different size deletions. Polymorphisms and Benign/ Likely Benign variants were not included in the analysis. By identifying new pathways, our study identified genetic causes for severity of appendicitis. It originates from abnormally differentiated myeloid progenitors as a result of numerous genetic events. Our study expands the clinical spectrum of SPATA5 mutations. Over time, case reports and recent largest review showed that females may be affected; haploinsufficiency was noted in 3; prenatal presentation in 6 unrelated fetuses (Frints 2019). According to the project design, DNA and clinical data form 3,270 participants were collected. Tubili: None. Lecouquierre: None. Alaix: None. Materials and Methods: aCGH analysis was performed on a DNA sample from a 5-year-old child using the Affymetrix® CytoScanTM 750K Array (Applied Biosystems). One of these genes is FOXC1, known to cause Axenfeld-Rieger syndrome. Meyn: None. These results show that the GalC7 hydrogel brings different and interesting conditions for inducing the differentiation and maturation of neural progenitor cells compared with polymer-based scaffolds or cell-only conditions. Habiloglu: None. Within the pediatric oncology context, promising preliminary results demonstrate that we can detect circulating tumor DNA (ctDNA) at frequencies down to one in one thousand with extreme accuracy. Conclusion: Our results highlight the importance of screening for DPY19L2 mutations in the absence of DPY19L2 deletions and strongly suggest that partial globozoospermia is not due to genetic defects on DPY19L2. The sources indicated a frequency of 12,2% for R882H in MDS, frequency in all our sample was 2,47 ± 1,72%, but patients with this mutation had diagnosed CML, not MDS. Background: The measurement of costs is challenging, but is fundamental in healthcare decision-making. The disease is multifactorial, caused by both genetic and environmental factors. With Miro Canvas, "on-demand" automation for WGS PCR-free protocols using mechanical fragmentation or tagmentation allows for more consistent, higher quality WGS libraries. Materials and Methods: We profiled the muscle biopsy splicing pattern of DMD exon 2 duplication in six DMD patients (identified by MLPA) using the Agilent High Sensitivity assay. Derhourhi: None. Patient's scores were relatively lower on independent living, mental health, relationship, self-worth, and senses. Several biologically plausible variants have been identified, but much work is required to establish the role of these genes in the pathogenesis of POP, or to establish a role for genetic testing in clinical practice. Zakharova: None. W.M. van der Flier: None. Results: We identified 5 known pathogenic/likely pathogenic missense variation types: p.Ile88Leu (77.9%, N = 74), p.Val50Met (12.6%, N = 12), p.Thr139Met (3.2%, N = 3), p.Phe84Leu (3.2%, N = 3), p.Val142Ile (N = 1). Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the development of multiple renal cysts causing renal enlargement and end-stage renal disease (ESRD) in 50% of patients by 60 years of age. Additionally, there is a much easier translation to a research setting, data reanalysis and collaboration with other centers in the remaining unsolved cases (additional 3 candidate genes so far). At the same time, phenotypic aging is a potential model for exploring the molecular mechanisms of aging. A functional study will be needed to conclusively determine effect of variant on the interaction of MLH1 and PMS2. Conclusion: The final diagnosis was male pseudo-hermaphroditism due to 5-alpha-reductase type 2 deficiency (OMIM#264600). We aimed to elucidate the genetic background of PTR. Kleefstra: None. Discussion: The present case has a 6.4Mb duplication in 8p11.23p11.1 region. CCA was performed accordingly with the International System for Human Cytogenomic Nomenclature 2016. Sandhu: None. Sadan: None. R.V. Boekel: None. P07.025.A Genotyping of Russian patients with RA using the targeted NGS panel Ekaterina A. Early pregnancy loss (EPL) occurs in ~ 15% of clinically-recognized pregnancies and is the most common complication of pregnancy. A significant proportion of osteosarcomas is associated with germline mutations in cancer predisposition genes. Varavallo: None. Çolak: None. Presence of a much milder clinical phenotype without epilepsy compared to the already reported mutation in the same amino acid causing a severe form of epileptic encephalopathy could be attributed to the different physicochemical properties of the mutant amino acids or imply the influence of modifying genetic factors. Genetics Department, Hospital Universitario La Paz, IdiPAZ, Madrid, Spain., Madrid, Spain, 7Bioinformatics Section. additional diagnostic tool for hereditary cancer), uses (pharmacogenetics vs. This study was supported by "Fondazione Italiana Sclerosi Multipla" [project 2013/R/13]. Vikkula: None. M.S.C. Wilson: None. Herrera-Pariente: None. Olaso: None. The aim of this study was to establish the frequency of the Y chromosome microdeletions in Turkish infertile men who referred to our center with severe oligozoospermia and azoospermia. RNP complexes consisted of SpCas9 protein (NEB) and sgRNA to EGFPwt or EGFPmut (Guide-it sgRNA IVT Kit, Takara Bio). WES result: TRPV4: heterozygous pathogenic missense variant c.806G>A, p.Arg269His. Consultant/Advisory Board; Modest; MSD, Bayer, Biocartis, Incyte, Roche, BMS, Merck, Thermofischer, Boehringer, Ingelheim, Astra Zeneca, Sanofi, Eli-Lilly. Stringent filtering based on 430 loci related to PID, internal quality control parameters, and the database of genomic variants. P02.045.B Novel stopgain variant in SOX2 gene causing autosomal dominant type 3 syndromic microphthalmia Florina Stoica 1, Adela Chirita-Emandi2, Andreea Ionescu2, Nicoleta Andreescu2, Maria Puiu2 1Ophthalmology Department, Emergency Clinical Municipal Hospital, Center of Genomic Medicine, University of Medicine and Pharmacy "Victor Babes", Timisoara, Romania, 2Center of Genomic Medicine, University of Medicine and Pharmacy "Victor Babes", Regional Center of Medical Genetics Timis, Clinical Emergency Hospital for Children "Louis Turcanu", part of ERN ITHACA, Timisoara, Romania. P01.059.C Prenatal diagnostics of NF2 mutation in the fetus, associated with the development of endometrial cancer Kalina Belemezova 1,2, Kunka Kamenarova3, Kalina Mihova3, Mariela Hristova-Savova1, Albena Todorova4, Radka Kaneva3, Ivanka Dimova1,3 1Genetic Laboratory, SAGBAL Dr. Shterev, Sofia, Bulgaria, 2Medical University of Sofia, Sofia, Bulgaria, 3Molecular Medicine Center, Medical University of Sofia, Sofia, Bulgaria, 4Laboratory Genika, Sofia, Bulgaria. We describe a three - generation family characterized by history of breast, gastric and bowel cancer, all histologically confirmed. AlShamsi9, N. Mitroi: None. Introduction: Social adaptation is the main ability for any schizophrenia patient and its family to judge whether the therapy is working or not, improving of social functioning is the mail goal to reach for healthcare professionals. To date, only 20 patients have been reported in the literature with 13 pathogenic variants. Campos-Barros: None. To determine if variants have a functional impact, our pipeline focuses on alternative splicing as well as the integration of exome and transcriptome data. CACNA1A thus represents a complex gene in clinical neurogenetics. Materials and Methods: A group of 172 cervical cancer patients was analyzed. Phenotypic and genotypic features were compared. Methods: The study included 902 DCM probands from the Maastricht Cardiomyopathy Registry, who underwent genetic testing. Girotto: None. Finally, we demonstrate that the double hemideletion Mvp::Mapk3 rescues NAPs and alters behavioral performances, suggesting that MVP and ERK share the same pathway, in vivo. Malignant plasma cells accumulate in bone marrow leading to bone marrow failure, also in extramedullary sites. Patients seen had diagnoses of SLE, periodic fever syndrome and atypical juvenile idiopathic arthritis in the main. P17.034.A Systematic and automated genotype-phenotype associations reassessment through ClinVar follow-up Kevin Yauy 1, Francois Lecoquierre2, Stephanie Baert-Desurmont2, Detlef Trost3, Aicha Boughalem3, Armelle Luscan3, Jean-Marc Costa3, Vanna Geromel4, Laure Raymond4, Pascale Richard5, Sophie Coutant6, Melanie Broutin7, Raphael Lanos7, Quentin Fort7, Stenzel Cackowski8, Quentin Testard1, Abdoulaye Diallo7, Nicolas Soirat7, Jean-Marc Holder7, Denis Bertrand7, Anne-Laure Bouge7, Sacha Beaumeunier7, Jerome Audoux7, David Genevieve9, Laurent Mesnard10, Gael Nicolas6, Julien Thevenon1, Nicolas Philippe7 1Institute of Advanced Biosciences, Centre de recherche UGA, Inserm U 1209, CNRS UMR 5309, Grenoble, France, 2Normandie Univ, UNIROUEN, Inserm U1245 and Rouen University Hospital, Department of Genetics and Reference Center for Developmental Disorders, Rouen, France, 3Laboratoire CERBA, Saint Ouen L'Aumone, France, 4Laboratoire Eurofins Biomnis, Lyon, France, 5AP-HP, DMU BIOGEM, UF Cardiogénétique et Myogénétique Moléculaire et Cellulaire, UMR_S 1166, Sorbonne Université and ICAN Institute, Hôpital Universitaire Pitié-Salpêtrière, Paris, France, 6Normandie Univ, UNIROUEN, Inserm U1245 and Rouen University Hospital, Department of Genetics and Reference Center for Developmental Disorders, F 76000, Normandy Center for Genomic and Personalized Medicine, Rouen, France, 7SeqOne, Montpellier, France, 8Inserm U1216, Grenoble Institut Neurosciences, GIN, Univ. Rare diseases, such as mucopolysaccharidosis (MPS) IVA (Morquio A syndrome) and MPS VI (Maroteaux-Lamy syndrome), are often misdiagnosed as other types of skeletal dysplasia (SD) or may go undiagnosed for extended periods, potentially resulting in delayed intervention and irreversible disease progression. Niessen, Joyce B. In 30 samples, two driver mutations were present in one sample, and we did not find any of mutations present in our panel in 9 patients. Supek: None. Kozlova, Dmitry A. Neuronal system pathways were subsequently found to be differentially enhanced in the pools. Their action needs however to be tightly controlled by a population of regulatory T cells (Treg) endowed with immunosuppressive function. A key genetic counseling goal is to facilitate informed decision making. Common categories for both gene sets were metabolic process, cellular process, localization and biological regulation, while transport, neurological system process and regulation of cellular process were additionally identified in biomarker gene set. The current CNA detection methodologies using NGS are based mainly on genome reads count coverage and its profile. Histopathological analysis showed myxoid degenerative changes of the abdominal aortic tissue. Cruchaga: None. Wilke: None. Given the number of patients without any variant (n = 135), we presume that a significant number of genes related to HSPs are yet to be uncovered. Stoneman: None. P12.051.C Multiplexed high-throughput MSREqPCR qualification of Colon Cancer DNA-methylation biomarkers in plasma cfDNA Andreas Weinhaeusel 1, Walter Pulverer1, Silvia Schönthaler1, Jasmin Huber1, Kristi Kruusmaa2, Bhangu Jagdeep Singh3, Klemens Vierlinger1 1AIT, Vienna, Austria, 2Universal Diagnostics S.L., Sevilla, Spain, 3Medical University of Vienna, Vienna, Austria. In the 1st trimester ultrasound, an increased nuchal translucency was identified, without other changes. Lactotransferrin (LTF) is a main salivary glycoprotein, which modulates the host immune-inflammatory and antibacterial response. V.V. Tsay: None. Hornemann: None. J.A. Sullivan: None. P16.016.C Mitochondrial DNA integrity of induced pluripotent stem cells (iPSCs): mandatory screen for unwanted variants before any use of iPSCs Flavia Palombo 1, Camille Peron2, Leonardo Caporali1, Angelo Iannielli3, Alessandra Maresca1, Ivano Di Meo2, Claudio Fiorini1,4, Alice Segnali2, Tiina Manninen5, Francesca L. In both SSCs the students learned the importance of thinking creatively and sensitively and to adapt their language and approach depending on the audience. P19.019.C Molecular spectrum of PCSK9-based FH in France, the French p.(Ser127Arg) founder variant Yara Azar 1,2,3, Yara Abou-Khalil1,2,3, Mathilde Di-Filippo4,5, Alain Carrié6, Sophie Béliard7, Catherine Boileau1,3,8, Marianne Abi-Fadel1,2, Jean-Pierre Rabès1,9, Mathilde Varret1,3 1LVTS, Inserm U1148, Bichat Hospital, Paris, France, 2Laboratory of Biochemistry and Molecular Therapies (LBTM), Faculty of Pharmacy, Pôle Technologie- Santé, Saint Joseph University, Beirut, Lebanon, 3Paris University, Paris, France, 4Department of Biochemistry and Molecular Biology, Hospices Civils de Lyon, Louis Pradel Cardiovascular Hospital, Bron, France, 5INSERM U1060, INSA de Lyon, INRA U1235, Univ Lyon-1, Université de Lyon, Villeurbanne, Oullins, France, 6Sorbonne University, UMR_1166 & ICAN; Department of Biochemistry, APHP. S.P. Deligiannis: None. One case, clinically classified as TBMN, had Dent disease genetically. Inflammation plays a key role in the development of complex diseases, such as cardiovascular diseases (CVDs). This variant is reported in dbSNP database (rs1599562180) and ClinVar Database as likely pathogenic. Perez Martin: None. Rangachev: None. The LCT locus associations seemed modulated by lactose intake, while those at ABO could be explained by participant blood type in interaction with the secretor status determined by their FUT2 genotype. Brain MRI was normal and a DaTSCAN revealed an asymmetric bilateral reduction of striatal tracer uptake. Breast cancer is no exception and major scientific advancements have been made in risk prediction and the tools used. Garcia-Giralt: None. van Rheenen: None. Des Portes: None. technological barriers (security, traceability and transparency, and interoperability). Materials and Methods: The disease was diagnosed through clinical features of MADB, assisted by radiologic and biochemical tests. Materials and Methods: The DeSIRe was developed by a multidisciplinary team using the International Patient Decision Aids Standards quality criteria and the Ottawa Decision Support Framework. No mutations have been identified in 34/128 (26,6%) patients. Manuel Montejo: None. Advantages of this technologies includes reducing patients travel time to medical centers and waiting time. The Tibetan population is well-known for high altitude adaptation. In total to date we have had submissions for >100,000 BRCA tests and >20,000 CRC/MMR gene tests. Davidenko: None. C.R. Cederroth: None. In embryonic mouse gonads, CXCL12 was shown to direct the migration of primordial germ cells (PGCs) to the gonadal ridges. Childs: None. Hamosh: None. K.J. van der Gaag: None. However, characteristic features of DDX3X-NDD are unspecific and hardly distinguishable from other intellectual disability syndromes, posing challenge to clinicians. Not surprisingly, the most common recurrent variant was m.3243A>G (40 patients with heteroplasmy levels ranging from 5.8 to 70.9%), which underlies maternally inherited diabetes, hearing loss, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). The variant was absent in the DNA extracted from the proband's peripheral blood and buccal brush, indicating its postzygotic origin. T.P. Melo: None. Anastasiadou: None. The mean CD was 24 years for controls and 27 years for women with PCOS. McLaughlin1 1Trinity College Dublin, Dublin 2, Ireland, 2University of Reading, Reading, United Kingdom. Laktionov: None. Deltas: None. Kolomiichenko2, LIlia Y. Francescatto: None. Baban: None. Finally, the project aims to provide a well-documented and easy-to-run pipeline, which automatically assigns a class to each variant and presents only a handful set of the relevant variants to the human curator. Statistical fine-mapping revealed 9 variants in the 95% credible set and functional annotation linked these to genes associated with malignant neoplasms, circulating cholesterol, and transmembrane proteins, suggesting an effect on cellular proliferation and cholesterol metabolism. Stuppia: None. Vitart: None. Observed elevated amount of matrix CLPP protease suggests the activation of the mitochondrial protein quality control machinery in UQCRC2Gly222Ala fibroblasts. Results: 49% of the participants were between 70-80 years old, 36% between 81-90, 14% over 90 years old. Velon: None. Baldassarri: None. We lost 3 cases due to technical problems.In all but one case, the quality of fetal brain tissue was good, as assessed in the gross dissection and in later histologic examination. Recently, murine model study showed that COMMD protein deficiency leads to a defect in the transport of ATP7B (copper membrane trasporter) from cytosolic vesicles to the plasma membrane, resulting in hepatic copper accumulation. Khneisser: None. Including those previously published, we identified 446 unique variants, among which 68 were novel, in 1190 subjects (including newborn screening positive subjects). Results: three genome-wide significant variants were associated with TFR: rs9397818A on chr6 increases the risk of an earlier relapse and has an eQTL effect in whole blood on TFB1M, key to mitochondrial gene expression, and TIAM2, implicated in endothelial function and cell migration; rs2071572A is a risk allele intronic to synaptotagminV, involved in exocytosis of secretory vesicles, with an eQTL effect in brain cortex; finally the risk allele rs6124768A maps to CD40 locus and increases its expression according to a public eQTL database. MLPA/CMA analysis identified compound heterozygous or homozygous deletions in 9 patients. Jiménez-Rolando: None. All 13 low penetrance CNVs with parental studies were inherited, these brought significant uncertainty to reports. M.L. Dentici: None. Since the orientation of the monomers with respect to each other plays a crucial role in the function of the protein, therefore, we hypothesize that TNNI3K-S511P might negatively affect the kinase activity of the protein. Results: Twenty-nine different RPE65 variants were identified in our cohort, 7 of them novel. We report a case of a nine-month old girl with delayed motor development (delays in sitting and holding head up), general hypotonia, dysmorphic facial features (prominent forehead, discrete strabismus) and noticeable happy demeanor. We analyzed the STK11 gene using deep targeted sequencing in 84 index cases. P01.031.C Exome sequencing in structurally normal fetuses - yield and dilemmas Hagit Daum, Tamar Harel, Shiri Gershon-Naamat, Adily Basal, Orly Elpeleg, Vardiella Meiner, Hagar Mor-Shaked Hadassah, Jerusalem, Israel. E.N. de Boer: None. Martinez-Jimenez: None. For Research Use Only. The phenotype was based on self-reported HL and ICD9/10 diagnosis for sensorineural HL. We then used protein extracts from whole brain preparations to generate protein abundance profiles using 2D-PAGE coupled with mass spectrometry for peptide identification and identified peptides corresponding to 25 unique proteins with >1.5-fold difference in abundance, including alpha-Tubulin. TBRS overlaps clinically with other overgrowth intellectual disability síndromes. Here we describe 5 factors and their possible impacts to evaluate before switching a clean-up chemistry. Congenital malformation of the skull are rare disease conditions, which may have severe impact on the life of patients. FGD1 gene encodes the FGD1 protein, a guanine nucleotide exchange factors, able to activate Rho GTPase cell division cycle 42 (CDC42). Study was supported by RFBR project №19-34-90072 and Russian Science Foundation (№18-15-00437). Introduction: Ectodermal dysplasia (ED) defines a group of genetic disorders characterized by developmental defects of 2 or more structures of ectodermal origin. Ribes: None. P04.057.B Clinical utility of a sponsored, no-cost skeletal dysplasia gene panel testing program: Results from 850 tests Guillermo Seratti 1, Vikram Pansare1, Tiffany Yar Pang1, Emanuela Izzo1, William Mackenzie2, Cathleen Raggio3, Klane White4, Rebecca Truty5, Britt Johnson5, Swaroop Aradhya5 1BioMarin Pharmaceutical Inc, Novato, CA, USA, 2Nemours Alfred I. Employment (full or part-time); Significant; Mendelics Genomic Analysis. These diseases are completely unknown to modern parents, and therefore they question the validity of preventive vaccination, especially since none of the vaccines is completely free of side effects. Damián: None. Deletions in PHKA2 are not frequent, but their study is necessary for the complete characterization of gene variants in patients with glycogenosis. Conclusions: TXNRD2 rs1139793 polymorphism may contribute to the identification of early-stage BC patients at a higher risk for disease recurrence and death. In one case, Silver-Russell syndrome was additionally diagnosed and one family had three cases of cleft palate. Fifteen (19.2%) of 78 donors had oocytes with PM errors. One Patient demonstrated 46,XX PHENOTYPIC MALE Karyotype. 13% of patients have mutation for alpha thalassemia represented by: -α3.7gene deletion (6%), αααα3.7 gene triplication (6%) and α2polyA-2(1%). Radiographically, ≈50% HET mice exhibit fractures and 96% of HMZ incur fractures at multiple ages. Gokpinar-Ili: None. Segregation studies were performed in each family. D'Amato: A. Multiplex Ligation-dependent Probe Amplification (MLPA) was performed to confirm results and investigate family members. Ten rare missense variants were identified in 15/46 (33%) families with MD in the OTOG gene. Results: KidneyNetwork can accurately predict kidney-specific gene functions and (kidney disease) phenotypes for disease-associated genes and applying it to exome-sequencing data of kidney disease patients allowed us to identify a promising candidate gene for kidney and liver cysts: ALG6. Sanz: None. R.M. van der Helm: None. However, both genders reported similar burden of damaging variants on the entire genome when considering only structural variants found in high constraint regions. V.S. Baranov: None. Perez-Hernandez: None. Her upper and lower limbs muscle power decreased ranging from 2 to 4/5. We identified proteins and biological pathways that might be uniquely altered in SD, by comparing to 9 other large FTD and Alzheimer's Disease (AD) proteomics datasets. Introduction: The rapid evolution of Medical Genetics as a speciality has resulted in significant diversity in training programmes and examination requirements. Winkler: None. Gamerdinger: None. Jensen: None. Seven patients has a molecular verification for the diagnosis X-linked agammaglobulinemia. In total, 164 primary findings were reported in 158 patients, representing an overall diagnostic yield of 31.6%. Compared to previous technologies, it is more reliable, easier and cheaper to use; even if serious technical problems still exist. Burger: None. The variant was calculated based upon observed versus expected coverage using exome sequencing data. Further analysis of pathogenic variants from ClinVar identified 961 variants localized in high-confidence microRNA-binding sites and only six variants were localized in 3'UTRs. For two of them we also performed an experimental test. Rodríguez-Fernández: None. We screened various IDs by methylation analysis for differentially methylated regions related to known IDs. We also performed clinical analysis. Results: From 23 patients clinically diagnosed with SMA, 22 had homozygous deletions of exons 7 and 8 of the SMN1 gene, while 1 patient had a normal number of copies of exon 8 in SMN1. de Tayrac: None. However, which genetic mechanisms modulate cytokine responses upon BCG vaccination and how they vary between Africans and Europeans are unknown. Ontiveros: None. Here we present a case that was solved with WGS in which all other methods used did not yield definite results. Consultant/Advisory Board; Modest; Amicus, BioMarin Pharmaceutical Inc, Orphan Disease Center, Sanofi, Sobi, Takeda, Ultragenyx, Denali, Inventiva, JCR, RegenXBio, Sigilon. P12.135.C Mosaic TP53 mutation in a patient with familial and personal history of breast, gastric and bowel cancers Emanuele Micaglio 1, Federico Romani1, Michelle Monasky1, Paola Carrera2, Monica Zanussi2, Giorgio Nevio Casari2, Filippo Martinelli Boneschi3, Silvia Presi2, Carlo Pappone1 1IRCCS Policlinico San Donato, San Donato Milanese, Italy, 2IRCCS San Raffaele Hospital, Milan, Italy, 3IRCCS Ospedale Maggiore Policlinico, Milan, Italy. Viñuela: None. Nalbant: None. The couple's first female child died at nine months due to complications of respiratory tract infection; she had severe global developmental impairment with hypotonia and infantile epilepsy. Toncheva: None. OGM was performed according to the manufacturer's instructions and samples were loaded on a Saphyr instrument. Bychkov: None. The aim of the study is to summarize our experience in establishing the diagnoses in dysmorphic children. Introduction: The need for genetic testing has grown in recent years. Botti: None. Results: A total of 262 responses were received from nurses (n =226, 86.1%) and midwives (n = 36, 13.7%) from six out of seven health boards across Wales. Antoniou9, Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA), Ovarian Tumor Tissue Analysis Consortium (OTTA), David Goldgar10, Amanda Spurdle11, Kyriaki Michailidou1,3 1Biostatistics Unit, the Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus, 2Department of Electron Microscopy and Molecular Pathology, the Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus, 3Cyprus School of Molecular Medicine, Nicosia, Cyprus, 4School of Women's and Children's Health, Faculty of Medicine, University of New South Wales, Sydney, Australia, 5Adult Cancer Program, Lowy Cancer Research Centre, University of New South Wales, Sydney, Australia, 6Monash University, Precision Medicine, School of Clinical Sciences at Monash Health, Clayton, Australia, 7Department of Clinical Pathology, The University of Melbourne, Melbourne, Australia, 8Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, Australia, 9Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, Cambridge, United Kingdom, 10Huntsman Cancer Institute, University of Utah School of Medicine, Department of Dermatology, Salt Lake City, UT, USA, 11Division of Genetics and Population Health, QIMR Berghofer Medical Research Institute, Brisbane, Australia. Duchamp: None. In a male patient, we identified a rare damaging variant [(NM_005211.3):c.2646_2654+6del]. Kawasaki-Oyama, Marlon F. Lan-Leung: None. However, up to now ESAM has not been associated to any disease. P03.044.D The importance of NGS data reanalysis and further functional analysis: an example of impaired phosphate metabolism Margarita Sharova 1, Svetlana Papizh2, Olga Levchenko1, Alexandra Filatova1, Andrey Marakhonov1, Anatoliy Tulpakov1, Mikhail Skoblov1 1Research Centre for Medical Genetics, Moscow, Russian Federation, 2Veltischev Research and Clinical Institute for Pediatrics of the Pirogov Russian National Research Medical University, Moscow, Russian Federation. Radvánszky: A. R.P. Kuiper: None. Introduction: Thrombocytopenia Absent Radius (TAR) syndrome is characterized by bilateral absent radii and thrombocytopenia, sometimes associated with other skeletal, cardiac and genitourinary anomalies. Results: We detected miR-196b-5p downregulated in both stages of endometriosis compared to the healthy controls (fold change = -19,28 for the early stage, fold change = -139,54 for the late stage). P04.014.C Sitting-to-standing height ratio is a sex-specific risk factor for chronic back pain Maxim B. P12.084.D Searching for novel fusion genes by RNA-Seq in follicular lymphomaMaria Pospelova1, Konstantin Danilov1, Ekaterina Bozhokina2,3, Yuriy Krivolapov2, Anna Gorbunova2, Igor Evsyukov 1 1ITMO University, Saint-Petersburg, Russian Federation, 2Mechnikov North-West State Medical University, Saint-Petersburg, Russian Federation, 3Institute of Cytology RAS, Saint Petersburg, Russian Federation. In WES analysis performed in rapid mode a de novo ATP1A3 mutation (R756H) was found. Swertz UMCG, Groningen, Netherlands. Conclusions: The accessibility to next-generation sequencing allows clinicians to save much time and cost in identifying the aetiology of rare diseases. Materials and Methods: Wistar rats, RNA-Seq, real-time RT-PCR, bioinformatics. Morel: None. Fatima: None. This study summarizes the variability and distribution of genes from our 1085 PGT-M cases during 2014-2021 highlights the shift towards rare disorders. Hastie: A. Popova: None. The patient has normal growth and mental abilities. No mutual disease-causing gene was identified however, candidate genes involved in preadipocyte differentiation (ATF2, CTSB, AKT2), adipogenesis (CDH13), tumour suppressor genes (PRDM2), and cell proliferation (PTPRZ1, TRIM24), were identified in single families. Nevertheless, several reports exist describing interindividual differences of the brain vulnerability to the toxic influence of hyperphenylalaninemia. The principal features are overgrowth and intellectual disability. Pohlova-Kucerova: None. Charoenyingwattana: E. The spectrum of revealed numerical karyotype abnormalities did not differ between the groups. Patient 1 is a 7-year-old girl with dysmorphic features including synophrys, flat nasal bridge, protruding ears, hirsutism, and brachydactyly. A.L. Danilova: None. Available tools still lack accuracy and sensitivity, complicating their use for studying role of microRNA-binding sites mutations in human disease. Similarly, CT scan and colonoscopy tracking also found no abnormalities. Altamura: None. S.W. Lukowski: None. Kocaturk-Sel: None. A.M.W. van de Ouweland: None. C.W. Yeh: None. Evidence levels and recommendation strengths were assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE). The proband's symptoms were progressive dysphagia, memory impairment, apraxia and spasticity. Van Diemen, Morris A. Subsequent molecular genetic testing in these family members showed that the two variants described above in the MMP13 gene also occur in them and thus segregate with the occurrence of the disease in the family. P11.121.C Analysis of exome data of a nationally identified cohort of 603 patients with syndromic orofacial clefting Kate Wilson 1, Dianne Newbury2, Usha Kini1,3 1Oxford Centre for Genomic Medicine, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom, 2Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, United Kingdom, 3Spires Cleft Centre, John Radcliffe Hospital, Oxford, United Kingdom. Brown: None. Bertrand5, K Khuller2, A. MDR was used to assess gene-gene relationships. P17.075.B Deciphering the role of trasposable elements in CD4+tumor-infiltrating lymphocytes at single cell resolution Valeria Ranzani 1, Benedetto Polimeni2,1, Annarita Putignano1, Samuele Notarbartolo1, Valeria Bevilacqua1, Serena Curti1, Sergio Abrignani1,3, Federica Marasca1, Beatrice Bodega1 1Istituto Nazionale Genetica Molecolare, Milano, Italy, 2University of Milano-Bicocca, Medicina Traslazionale e Molecolare (DIMET), Milano, Italy, 3University of Milan, Department of Clinical Sciences and Community Health, Milano, Italy. P01.065.A Evaluation of the Telomere Length and its Effect on the Ovarian Reserve in a Sample of Colombian Women Johana Marin Suarez 1, Harold Moreno-Ortiz2, Lissette Otero3, Stephen Matlin3, Clara Inés Esteban-Pérez2, Maribel Forero-Castro1 1Universidad Pedagogica y Tecnologica de Colombia, Tunja, Colombia, 2Departamento Biogenética reproductiva. We contrast a curated set of 406 regulatory variants causative for Mendelian disorders and millions of human-derived sequence alterations (as proxy for non-pathogenic variation) in the human genome. A.J. Wallace: None. Kidney exhibited a distinct transcriptomic signature. We hypothesize that the identified differences could be associated with region-specific plasticity mechanisms in learning and memory processes. Cantello: None. Measures include empowerment (Genetic Counselling Outcome Scale, GCOS), knowledge, risk perception, emotional distress, screening/surveillance behaviours, perceived social support, decisional conflict and quality of life. Kocak: None. Introduction: We evaluated the potential of standard genotyping arrays for diagnostic purposes in a clinical setting. The G allele of rs533984 has been previously confirmed as favourable for surviving to very old age in Danish females. Precision medicine has been forecasted to change modern healthcare aiming to provide treatment options targeted towards the patient's genomic profile. The family history is unremarkable. Rodriguez-Revenga: None. Consultant/Advisory Board; Modest; AstraZeneca, MSD, Tesaro, Roche, GenMab, Pfizer, Clovis Oncology. This technique has made us progress in the understanding of CNVs with their impact on TADs (topologically associated domains). Therefore, the new mutations reported and their clinical relevance is important. Employment (full or part-time); Modest; PolyKnomics. Wilson1,3, Lucija Klaric3 1Usher Institute (University of Edinburgh), Edinburgh, United Kingdom, 2Genos Glycoscience Research Laboratory, Zagreb, Croatia, 3MRC Human Genetics Unit, Institute for Genetics and Cancer (University of Edinburgh), Edinburgh, United Kingdom, 4Faculty of Pharmacy and Biochemistry (University of Zagreb), Zagreb, Croatia. NIPT uptake increased to 43.4% in 2018. A workshop was held in February 2020 to agree a draft outline, identify contents and the process for generating the draft. Introduction: Anaplastic lymphoma kinase (ALK) gene translocation within chromosome 2 results in EML4-ALK oncofusion, drivers for lung adenocarcinoma (LUAD). This suggests the possibility that haploinsufficiency of TBCK can have phenotypic effect in human hets. Dieux: None. Patients were stratified into moderate and good or poor (n = 233) social functioning groups. A total of 208 HSP patients (and 79 affected relatives) were successfully characterized: 118 by single-gene testing, 78 using multigene panels and 12 through larger NGS panels (e.g., clinical exome). We also observed more severe clinical phenotype in the deletion type ARS. Riedijk: None. Conclusion: NGS panel analyses identified mutations within the TGM1 gene in 52.7% of studied families prioritizing it as a target gene for future molecular analyses among Egyptian ARCI patients. The results warrant future validation. At the same time, tools that showed best performance also displayed lower dependence on sequence-based confounders, sequencing technology (WES vs WGS), and coverage. ID and ASD symptoms are often overlapping. N.A. Vicdan: None. Introduction: Mitochondrial diseases are a heterogeneous group of disorders caused by mitochondrial dysfunction. LF UK) and University Hospital Motol, Prague, Czech Republic, 4Department of Neuromuscular Disorders, UCL Queen Square Institute of Neurology, London, United Kingdom. Retrospective reanalysis of nonNCCN-HBOC FA genes (FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, SLX4, ERCC4) was performed on 2023 individuals from different HBOC families. No BRCA1 or BRCA2 mutations were detected in the examined group. M.A. Amelina: None. Low or high intolerance of uncertainty was not associated with reporting decisions. APOGeE is ITHACA's main contribution to the EU strategic objectives of ERN-specific knowledge generation, to contribute to a structured programme of post-graduate education and training in the field of human genetics and Rare Disorders. Our pilot study included 20 families (trios or quatros) of children with severe NDDs and associated congenital abnormalities. FJD Biobank, IIS - University Hospital Fundación Jiménez Díaz, Universidad Autónoma de Madrid (IIS-FJD-UAM), Madrid, Spain, 6Biobank Platform IMIB-Arrixaca, Murcia, Spain, 7Medical Genetics Department. Introduction: Immune receptors repertoire (TCR/BCR) profiling is a powerful source of basic and applied insights in immunogenetics. Phenotypic Features like Height, Weight, Head Circumference were recorded. A.K. Bergmann: None. Beaudouin: None. The coding region of the GLYAT gene was found to be highly conserved and the rare S156C199 variant negatively affected the relative enzyme activity and kcat parameter. The rs429358 APOE allele, which is known to significantly increase AD risk, is also found as one of the two pathogenic variants in healthy young individuals. Methods: Genotyping results with the Global Screening Array (Illumina GSA-24 v.2.0 or v3.0+Multi-Disease content) were assessed in 530 independently sequenced diagnostic DNA samples for 29 clinical indications involving 55 different genes and 129 different variants. Pomegranate extract (1.2, 2.4 %), garlic (0.5, 1.2 %), grape seeds (1.2, 2.4 %) were used. Analysis allowed to genetically-characterizing additional 14 patients, found to be mutated in ciliary genes related to skeletal ciliopathies other than EvC. Melegh: None. P04.023.D Analysis of novel splice site variants in craniosynostosis causing genes Angela Borst 1, Tillmann Schweitzer2, Denise Horn3, Erdmute Kunstmann1, Eva Klopocki1 1Institute of Human Genetics University of Wuerzburg, Würzburg, Germany, 2Department of Pediatric Neurosurgery University Hospital of Wuerzburg, Würzburg, Germany, 3Institute for Medical and Human Genetics Charité Universitätsmedizin Berlin, Berlin, Germany. In all patients, somatic DNA from the FFPE ovarian tumour was analyzed by the Oncomine BRCA Expanded NGS panel (ThermoFisher) and a commercial bioinformatic pipeline. Introduction: Laryngeal squamous cell carcinoma (LSCC) is an aggressive malignancy with poor prognosis, which despite modern treatment protocols, novel molecular markers are required to improve survival. Ellinor: None. Conclusions: This efficient QF-PCR/aCGH/MLPA strategy has a lower failure rate and higher diagnostic yield than karyotype. Crujeiras: None. K.K. Kandaswamy: A. Tallila: A. Results: Splicing vectors with different genomic context, several promoters of varying strength, containing different exons were created in order to reproduce the wild-type splicing pattern of the SCN1A gene. Eryilmaz: None. Gene regulation depends on cis-regulatory elements which can interact with gene promoter by chromatin loop. Results: Our guidelines offer a decisional algorithm built on 3 key principles: (i) the recommended annual assessment of all techniques and technological platforms, if possible through EQAs covering the technique, genotyping and interpretation, (ii) the triennial assessment of the genotyping and interpretation of specific germline mutations and pharmacogenomics analyses, (iii) the documentation of actions undertaken in the case of poor performances and the participation to a quality control the following year. Dietze-Armana: None. Materials and Methods: A case-control study with 235 Northern Spanish patients: 55 XFS patients and 180 controls. Introduction: Recent genome-wide association studies have reported that neuroticism is influenced by about 600 genes. P20.019.B Hydralazine promotes the expression of pluripotency genes OCT4 and NANOG in human somatic cells Alain Aguirre-Vazquez 1,2, Fabiola Castorena-Torres3, Luis A Salazar-Olivo1, Mario Bermúdez de León2 1Instituto Potosino de Investigación Científica y Tecnológica, San Luis Potosí, Mexico, 2Centro de Investigación Biomédica del Noreste, Instituto Mexicano del Seguro Social, Monterrey, Mexico, 3Tecnologico de Monterrey, Escuela de Medicina y Ciencias de la Salud, Monterrey, Mexico. We then show the analysis of serum transthyretin levels in the TTRV30M carriers from the endemic foci of Mallorca. Results: A total of 24 CNVs in 23 patients were validated. PUVA treatment elevated transcription level of GATA3, STAT5B, and JAK1 on 62-75% of patients; JAK3, STAT1, STAT4 and FOXP3 expression is decreased in 75-85% of patients. P07.029.A Molecular spectrum of Von Willebrand Disease Type 3 Esra Isik 1, Durdugul Ayyildiz Emecen1, Kaan Kavakli1, Fahri Sahin1, Enise Avci Durmusalioglu1, Canan Albayrak2, Melike Evim3, Ekrem Unal4, Fatma B. Moreover, B-ALL samples showing higher total LEF1 expression had significantly shorter relapse-free survival (p = 0.008) and overall survival (p = 0.011). Garcia-Pelaez: None. Patients in the intermediate and high genetic risk group were associated with a 2.50-fold (odds ratio [OR] 2.50; 95% confidence interval [CI]: 0.92-6.81; P = 0.07) and 2.70-fold (OR 2.70; 95% [CI]: 1.13-6.43; P = 0.02) increase in AF risk compared to the low risk group. The in-frame deletion lacks eight amino acid residues including two phosphorylation sites, which were evolutionary conserved. In a pilot study, we report exome sequencing results from a subset of 17 families with 38 affected. Candidate genes associated with non-syndromic OFCs were defined based on data from prior genome-wide association studies, while genes causing established OFC-syndromes (autosomal dominant (AD) and autosomal recessive) were retrieved from the literature. Results: Electron microscopy studies showed that the GBM of the 4-PBA treated AS mice after the 6-12-month treatment has a considerable improvement in the morphology, compared with placebo-treated or TUDCA-treated mice AS mice. Conclusion: Our findings support a locus on 19p13.11 associated with neurodevelopmental disorder and variable malformations. Here we present a case of a boy with 2 episodes of severe hypotonia with depressed deep tendon reflexes and speech disorder, strabismus and ataxia triggered by a febrile infection. Fetal ultrasound revealed micromelia, narrow chest, prominent abdomen, brachydactyly, talipes, polyhydramnios. P12.090.B Solving the genetic aetiology of hereditary gastrointestinal cancer - a collaborative multicentre endeavour within the project Solve-RD Anna K. The disease is classified into 3 subtypes due to the qualitative or quantitative disorder of von Willebrand factor. Results: MID1 gene variations were found in 22 individuals (21 male and 1 female). Lurie Children's Hospital of Chicago, Chicago, IL, USA, Chicago, IL, USA, 3Department of Veterinary Medicine, Faculty of Animal Science and Food Engineering, University of São Paulo, Pirassununga, São Paulo, Brazil, 4Murdoch Children's Research Institute, Royal Children's Hospital and Department of Pediatrics, University of Melbourne, Melbourne VIC, Melbourne, Australia, 5Department of endocrinology and reproductive medicine, center for rare endocrine and gynecological diseases, Sorbonne Université Pitié Salpêtrière Hospital, Paris, France, 6BGI-Shenzhen, Shenzhen, China, 7Stanley Manne Children's Research Institute, Ann & Robert H. Results: We have recruited 18 fetuses (55,5% affected from aneuploidies) in the first year. Finally, in two probands and two of their relatives (mean age 33 years [range 15-54 years] 3 females), also all without cancer, the SMARCA4 variant was an incidental finding. P14.026.C Expanding phenotype in a patient with partial trisomy 13q/monosomy 3p resulting from a paternal reciprocal 3p;13q translocation Monica Martin-DeSaro 1, Lautaro Plaza-Benhumea2, Luz Gonzalez-Huerta3, Olga Messina-Baas4, Sergio Cuevas-Covarrubias5 1Medical Genetics Department, Hospital Materno Infantil ISSEMyM, EdoMex, Mexico, 2dHospital Perinatal, Monica Pretelini, EdoMex, Mexico, 3Hospital General de México, EdoMex, Mexico, 4Hospital General de Mexico, CDCMX, Mexico, 5Hospital General de Mexico, Universidad Nacional Autonoma de Mexico, CDMX, Mexico. Kayser: None. Review of medical records of patients with a molecularly confirmed NS diagnosis. MET c.3389T>C p.(Leu1130Ser) was not reported in databases. Asensio Landa: None. Recessive mutations in genes encoding members of the Fraser complex (FC) or associated proteins constitute an established genetic cause of Fraser syndrome in its three forms related to mutations in three different genes FRAS1, FREM2, and GRIP1 resulting in failure of the apoptosis program and disruption of the epithelial-mesenchymal interactions during embryonic development. After rigorous analysis of nuclear genome variants, 21 families had been diagnosed with either a known or novel monogenic disorders, while the other 34 remained undiagnosed. Irving: None. Salem: None. The intention is that this guidance is useable and readable for the expanding non genetic community undertaking genomic tests as well as for existing audiences. Ruseva: None. Artola: None. De novo (Dn) variants affecting protein-coding DNA are a well-established cause of Rare Diseases (RDs) in patients with a neurological/neurodevelopmental (NND) phenotype but their evaluation across the full-spectrum of clinical RD phenotypes has not been performed at scale. OVOL2 is a transcription factor acting as a repressor of ZEB1. Results: Genotyping of the SLC7A5 (LAT1) gene identified 17 wild type individuals, 12 heterozygotes and one homozygote with regard to the rs113883650 variant. Grant support: SAF2015-68016-R, AY12-2018 2019/0042, CB16/12/00234 F. P06.013.B Genetic study of MTHFR and LPA in patients with familial hypercholesterolemiaElena Sevilla1,2, Carmen Rodríguez-Jiménez1,2, Francisco Arrieta3,4,5, Javier Sanguino1,2, Amanda Herranz-Cecilia1,2, Ana Carazo1,2, Itsaso Losantos-García6, J M. Peldova: None. Most frequent pathogenic variant was p.E191K in exon 6. Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain, 2Centro de Bioquímica y Genética Clínica. Cerqueira: None. We described two families that exemplify these aspects.The first family (F1) displayed a sibship with 2 constitutional mismatch repair deficiency (CMMRD) patients and a family history of colon cancer in the maternal branch only. Lubys: A. Homozygotes 23525AA have an increased risk of delayed sexual development during puberty (OR = 1.38 CI 1.1-2.78). An individual diet was developed, the nature of changes in biomarkers confirming the disorder (level of amino acids, organic acids, trace elements, carbohydrates, metals, vitamins), which provided evidence of treatment, constant monitoring of specialists. Martinez-Monseny 1, Lourdes R. We report the experience of our research laboratory in the last five years (2015-2020), focusing on mutation analysis. The main genes targeted are SMN1, SMN2, and other genes from this region that may influence the phenotype. Materials and Methods: In this experiment, we analyzed two sets of gene-pseudogene systems, GBA and CYP, that are the second and eighth most common carrier disease alleles, respectively. Salinas: None. Introduction: Incidental findings are unintentionally uncovered pathogenic variants predisposing to a disease unrelated to the clinical question. Alders: None. In conclusion, our findings suggest a compensatory mechanism for aberrant HSP47-R222S binding, eventually leading to overmodification of type I (pro)collagen chains, thereby underscoring the importance of HSP47 for proper posttranslational modification and providing insights into the molecular pathomechanisms of the p.(R222S) alteration in HSP47, which leads to a severe OI phenotype. Menzies: None. Capron: None. Four patients have heterozygous variants in the FOXC1 gene: two novel (NM_001453.2:c.246C>A, c.235C>T) and two previously described (c.379C>T, c.379C>T). A.M. Gzgzyan: None. This research is supported by the grant from the National Centre for Research and Development no DOB-BIO10/06/01/2019. The allele detection rate for cystic fibrosis (75%) was lower because of non-inclusion of relevant variants on the array. DNA isolation was carried out using the standard phenol-chloroform extraction method. After prioritizing the genes, promising candidate genes for SPS that harbor potential biallelic variants include among others ANKRD17, LAMA5 as well as MCM3 while genes that harbor heterozygous variants include CDKN1A, CEACAM1, and PTPRT. Pérez-Tomás1, P Carbonell-Meseguer5,2, C Salcedo-Cánovas6, E Guillén-Navarro1,2,4 1Sección de Genética Molecular (Centro de Bioquímica y Genética Clínica), Sección de Genética Médica (Servicio de Pediatría), Hospital Clínico Universitario Virgen de la Arrixaca. Rickers: A. Funding: This work was financially supported by the project ID J3-9258 from the Slovenian Research Agency and Ministry of Education, Science and Sport C3330-19-952026. V.M. Kozlova: None. Sharma: A. P20.047.B Identification of novel SCN5A regulatory regions using a CRISPRi system in hiPSC-derived cardiomyocytes Adrian Pérez-Agustín 1,2, Hector Hugo Galvez-Leon2, Sara Pagans1,2 1Department of Medical Sciences. Simulation studies of two traits measured in a single cohort with varying sample size, varying trait correlation, and varying proportion of missing data from one trait demonstrate that flashfm reduces the set of potential causal variants by 30% compared to single-trait fine-mapping when traits share a causal variant; when there are no shared causal variants flashfm has similar results to single-trait fine-mapping. Patients were screened for PKD1 and PKD2 genes using Long Range PCR and Sanger sequencing or Nextera™ Technology for NGS. Smol: None. Like other SOX proteins, SOX4 contains a highly conserved high mobility group (HMG) domain that mediates DNA binding, bending and nuclear trafficking. Of all these patients, 56.75% (42/74) had the frameshift deltaF508 mutation, followed by other common mutations in the studied group, such as the G551D, the R553X or the R1158X variants. Rodríguez-Moranta: None. C.M. Kehoe: None. Genotype-first approach assures not only the earliest diagnosis of trisomy 21 (the most prevalent chromosome aberration), but also completion of the screening at 12–14 weeks. The prognostic impact of a drop higher than 10% was then investigated for the different fragments of ACTB in terms of PFS. This is a substantial improvement over using only sex, which has an AUC of 0.75. Some medical centers offer parents the choice if to be informed about these findings. Plon: None. Mühlegger: None. Sistonen: A. Exome sequencing was performed with SureSelect Clinical Research Exome and data analysed with SureCall (Agilent) and ClinicalVarsome (Saphetor). Mundlos: None. Compared to other regulated professions, the route towards legal recognition for genetic counsellors may be challenging due to its small number of practitioners. Materials and Methods: Mitochondrial DNA was sequenced (Illumina technology) in 170 individuals belonging to different Daghestani ethnicities. Introduction: Nurses and midwives are the largest professional group within the NHS, numbering 32,927 and making up 42% of the NHS health workforce in Wales in 2018. Hristova-Savova: None. Maher8, Emma R. France has its own vision of bioethics and thus has adopted specific laws on bioethics covering advances in biology and medicine. DSCs were obtained by Laser capture microdissection. Finally, (3) 14 pathologies resulted in being more frequent in OR-HKO individuals (p-value A of the IL10 gene between seronegative children and children with IgG to EBV were found. Demirhan: None. Makeev: None. According to various authors, about 8-10% of ADPKD cases do not have pathogenic variant in PKD1/2 genes. The Belgian consortium in prenatal diagnosis (BEMAPRE) defined SNP-array as the first-tier diagnostic approach for congenital malformation (Vanakker 2013). Employment (full or part-time); Significant; Blueprint Genetics. P03.004.A Delineation of the phenotypic and genotypic spectrum of type-IV-collagen-related nephropathy - Alport syndrome and thin basement membrane nephropathy Korbinian M. The current work-up includes testing of relatives to determine the zygosity of assumed biallelic variants, analyzing the segregation with the phenotype, and functional analyses of the most interesting variants. Results: The analysis of genomics in brain-specific and lymphocyte-specific interactomes revealed a series of genes that carry variants and form significant gene networks; these networks share a common component, but let us also hypothesize tissue-specific effects on different pathways. In fact, cancer is the most common cause of death in diabetes. Binary protein-protein interactions between PMS2 and variants of MLH1 were investigated using Y2H and 3-amino-1,2,4-triazole (3-AT) gradient. Locatelli: None. Marinova: None. Introduction: Our experiments showed that the DNA-demethylating epigenetic drug 5-azacytidine (5azaC) is a teratogen causing oxidative stress and intrauterine growth restriction (IUGR), alleviated in rat fetuses by an antioxidant-pretreatment. Introduction: Syndromic craniosynostosis is a genetically determined premature ossification and closure of one or more of the cranial sutures. K., D. As a consequence these patients are radiosensitive and present with increased cancer risk. Funding: J.A.L.E. is partially funded by INT18/00031 from ISCIII. All individuals presented with overgrowth, typical dysmorphic features and different degrees of intellectual disability. Modzelewska: None. Typically, affected males have a contiguous gene syndrome, which includes phenotypic features of different disorders. A molecular basis was identified in 16/32 pedigrees. Antunes2, Cristina Catarino3, Manuel Campos4, Teresa Almeida8, Sara B. Conclusions: We have identified a variant in TRAF2 and a deletion which include KDR. Vosberg: None. Background: In Noonan syndrome(NS), the treatment with growth hormone(GH) has been carried out in the last decades, with reported effects on improvement of growth velocity and adult height, however, these data usually included patients with NS phenotype, only the last few years bringing data about GH treatment in genotyped NS patients.Aim.To evaluate the effect of GH treatment according to genotype in patients with NS, by a systematic review of the literature. In high grade serous OC patients, the most commonly mutated genes were BRCA1 and TP53, while in early stage non-serous OC and EC patients PIK3CA, PTEN, KRAS and ARID1A mutations were the most common. Filippova: None. Ayvazyan: None. Methods: We inquired all Portuguese medical genetics departments, collected clinical data and compared with previous described cases. J.B. Melo: None. 20 children were with known S. Di Pierro: None. Another proven father carried the hemizygous splice-donor variant c.459+1G>A in TEX13B. Sansović: None. Most of the patients with XGS have a heterozygous loss-of-function AHDC1 mutations. Seif Ali: None. Landgraf: None. Mazzini: None. Gruode: None. Employment (full or part-time); Significant; Blueprint Genetics Inc, a Quest Diagnostics Company. Results: p.Arg21Ter (carrier frequency: 1.6-2.1%) occurs on medium sized LPA alleles and associated with lower Lp(a) (β = -11.7 mg/dL [-15.5;-7.8], p = 3.39e-32) in a fixed-effect linear regression meta-analysis. G.J. Maher: None. This data also suggests the use of recombinant CRISPs may be of benefit in assisted reproductive technologies. Embryonic viability was defined as the ability of an embryo to implant and give a viable pregnancy. Froufe: None. Results: Frequent upper respiratory tract infections were recorded in 2 patients (2.89%), psoriasis was diagnosed in 1 (1.45%), as well as alopecia. Many of these defects lead to multi-systemic manifestations, commonly involving the central nervous system. Description of further patients with similar findings would be needed to draw any inferences. Results: A homozygous frameshift variant c.807_810delCTGT;p.(Cys270Serfs*33) was identified in the patient. allow us to obtain numerical characteristics comparing populations.In the study we used 533313 surnames from the voter lists and a total sample of marriage records for 1990-2000 throughout the Republic of North Ossetia. Introduction: Alpha-1 Antitrypsin deficiency (AATD) is an inherited condition characterized by reduced levels of serum AAT due to mutations in SERPINA1 gene. Results: The CPEO prevalence in Emilia-Romagna was 2.32/100.000, reaching 5.07 in Bologna province. Here we report two cases of arthrogryposis multiplex congenita (MIM: 208100), which presented at birth through hypertony, as a new phenotypic presentation of pathogenic variants in FLNC. Supported by MUNI/A/1595/2020, MUNI/IGA/1640/2020, AZV NU21-08-00237, and MH-CZ RVO 65269705. This study was financially supported by a Russian Science Foundation grant 19-75-20033. Thus, it is essential to use an ambitious strategy, including all genes related to cardiac excitability, to clarify the pathophysiological basis of VF in AMI. Stancheva1, Dora Marinova2, Evgeni Mekov3, Yanina Slavova-Marinova2, Vanio Mitev1, Radka Kaneva1 1Molecular Medicine Center,Department of Medical Chemistry and Biochemistry, Medical Faculty, Sofia, Bulgaria, 2University hospital "Medika", Ruse, Bulgaria, 3Clinical Center for Lung Diseases, Medical Faculty, Medical University of Sofia, Sofia, Bulgaria. Miro Canvas libraries demonstrated equivalent or better sequencing metrics compared to both manual efforts and a high-throughput plate-based liquid handler using the same kit. M.A. Grootenhuis: None. 4 tested variants showed no splicing change, although being reported as pathogenic or likely pathogenic in the literature. Introduction: Schuurs-Hoeijmakers Syndrome (SHS, OMIM #615009) is a rare cause of developmental delay with distinctive dysmorphic features. Although further functional studies are needed, this study adds a fifth rhodopsin mutation associated with CSNB. Tuscany Region "Bando Ricerca COVID-19 Toscana" 2020. Rodríguez Peña: None. Histological characterization, MMR protein immunohistochemistry (IHC) were performed in target tissues and hs-MSI metrics were calculated in a subset of cases. Pathogenic APC variants are causative for Familial adenomatous polyposis, a colorectal cancer predisposition syndrome. Introduction: Major depressive disorder (MDD), bipolar disorder (BD), schizophrenia (SCZ), and schizoaffective disorder (SZA) are a group of psychiatric disorders with a considerable amount of phenotypic and genetic overlap. Major manifestations are diarrhea, abdominal pain, weight loss with or without fever. Sensitivity analyses using different control cohorts and synonymous variants supported our results. All affected individuals had developmental delays including delayed speech development. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Modest; BioMarin Pharmaceutical Inc, Sanofi-Genzyme, Takeda. Interestingly, this patient carries the same LAMA2 loss-of-function mutation as a severely affected sibling. Urnikyte: None. Introduction: The genes that are commonly expressed in different tissue types are called housekeeping genes. SCD most commonly occurs in patients with coronary heart disease, whereas inherited cardiomyopathies and primary electrical disorders prevail in younger SCD victims (up to 30% of all SCD in the young). Delhomelle: None. Ketteler: None. Capó-García: None. Results: We applied FTAS-seq to study TMPRSS2-ERG fusion transcripts in prostate cancer cell line NCI-H660 to validate the approach. Consultant/Advisory Board; Modest; UCB Pharma, Esai, Xenon, Ionis, Upsher-Smith, Praxis, Sarepta, Disruptive Nutrition. Wasag: None. de Haro: None. The target height was -0.6SD. Conversely, even if the causality exists, its magnitude is not clinically significant since it has not been detected using such large datasets. We realize a whole genome sequencing with HiSeq 4000 by IntegraGen Genomics. Material and methods: 30X short-read Illumina paired-end WGS was performed in the proband and inversion breakpoints were confirmed by PCR of the specific fragment junctions and Sanger sequencing. Cibulková: None. Ramzan: None. Sanger and long-read sequencing respectively confirmed the variants. In the third Lebanese family, c.535T>C and c.787G>A were both present as heterozygous composite variants. Conclusions: The Hungarian Genomic Data Warehouse provides insight into molecular diagnostics, from individual common polymorphisms, through population-specific variants, to private, individual-specific mutations. Benistan: None. HbA2 and HbF levels were determined by HPLC. P19.029.A Wide spectrum of F9 variants in hemophilia B families from the Portuguese population Isabel Moreira 1, Maria J. Romagnoli: None. In the microarray analysis performed on this, it was confirmed that there was a deletion in the chromosome 13q21.1q31.1 region. Bijlsma3, A van Hagen4, M Heijligers5, S M. The younger patient has a normal sleep study and brain MRI scan. P09.110.C Functional analysis of PLXNA1 variants in a novel neurodevelopmental syndrome with oculo-cerebral anomalies Paulina Z. Coppola: None. Abid Mzid: None. Schweitzer: None. The miRNAs targeting the genes encoding 10 hub proteins were miR514b-3p, miR495-3p, miR3913-5p, miR4420, miR4789-5p, miR4500, miR4725-3p, miRNA-374b-5p, miR-196a-1-3p, miR5011-5p. Tissue specificity and colocalization analysis highlight the relevance of skeletal muscle in CWP. Drakulic: None. In particular, a 34-kb highly restricted DS critical region (HR-DSCR) has been identified as the minimal region whose duplication is shared by all PT21 subjects diagnosed with DS, while it is absent in all PT21 non-DS subjects reported in the literature up to 2017. Bahi-Buisson: None. Goel: None. Cohen20, Yili Xie21, Sureni V. Pipelines portability is ensured by project-related virtual environments including all required tools and dependencies. This study provides the largest to-date survey of genetic variation in Ukraine, creating a public reference resource aiming to provide data for historic and medical research in a large understudied population. Introduction: At our EMC we have initiated the GOALL project (Genotyping On All Patients), in which we investigate the use of high throughput SNP arrays for improving clinical care and making personalized medicine available to a larger public. Buniello: None. Among 1197 DEGs (with adjusted p-value A) associated with familial Mediterranean fever. Tikhonov, Olga G. Fetal fraction was determined using ZFY or a paternally inherited SNP for pregnancies bearing male and female fetuses, respectively. The weighted HLA-risk score (wHRS) was calculated for each individual. Bik-Multanowska: None. Facial features, nonspecific, in all: depressed nasal bridge, thin upper lip and horizontal eyebrows. The results of the study showed that the TL in patients with coronary artery disease before surgery and after 5 years statistically significantly differed from the TL of healthy people by 7 times (p < 0.05). Holcar: None. Laurie: None. Sanderson: None. Conclusions: Biallelic loss-of-function P4HTM variants were shown to cause HIDEA syndrome. In the case of this mutation (p.Pro380Ser) we confirmed the paternal inheritance of the mutation in the parental study. Introduction: Sudden infant death with dysgenesis of the testes syndrome (SIDDT) is a rare autosomal recessive disorder associating developmental sex disorder (DSD) in patients with 46,XY karyotype and visceroautonomic dysfunction responsible for sudden death before twelve months of age. Both these cohorts were compared to a control group of 5088 healthy individuals. Results: The consortium wishes to use a common protocol and to set up follow-up meetings to optimize the sharing of knowledge around the efficacy and tolerance of Imatinib in KOGS, but also administrative/ethical issues. J.L. Molinuevo: None. Introduction: Facioscapulohumeral muscular dystrophy (FSHD; OMIM*158900) is an autosomal dominant muscular disorder characterized by slowly progressive dysfunction of facial, upper and lower extremity muscles. This ability depends on the CCD2 domain integrity and I669Sfs*, falling within that protein portion, could cause the accumulation of protein aggregates. Our results indicate that considering the age at onset of ischemic stroke identifies genetic variants involved in disease accelerating processes. R.M. Reis: None. Next-generation sequencing was performed on MiSeq/Illumina platform with a panel of 94 cancer related genes. Migliorero: None. Data analysis and variant annotations were done with SOPHiA AI™ and SOPHiA DDM™ (SOPHiA GENETICS). Genotyping was performed with HRM (High Resolution Melt) method. demonstrated that obscurin activity varies and is an important mediator during myocardial hypertrophy. Monckton3, Maria A. J.M. Biard: None. Considering SEM occurrence and asbestos exposure levels may allow clinicians to better evaluate MPM risk. In addition, GestaltMatcher successfully detected similarities of facial features between patients. 53.7% had a history of at least one sports injury, namely sprains, bone fractures, muscle, or other injuries. M.J. Dixon: None. Poyatos-Andújar: None. T.H. van Prooije: None. Ballabio: None. To elucidate the underlying molecular mechanisms and to better understand the broad phenotypic spectrum of SHOX-deficiency, we analyzed differentially expressed genes in human fibroblasts (NHDF), where SHOX is expressed at detectable level. Both osteoporosis and high bone mass (HBM) are heritable and their genetic architecture encompasses polygenic inheritance of common variants and some cases of monogenic highly penetrant variants in causal genes. In published cases, the constant features characterizing STAG1 gene variants are developmental delay, recognizable facial gestalt and variable associated features.Case report: The proband was born at term by CS due to fetal hypoxia, her birth weight was 3220g, length 52cm, OFC 33cm (-1.75 SD). Zuccalà: None. To validate the consequences of the splice site variants on correct transcript splicing, we performed in vitro splice assays with mutation-matched minigene constructs in U2OS cells. Urothelial carcinomas are the 9th most common type of cancer worldwide. Kayserili Karabey: None. Genes and proteins of some transmitter systems were positively correlated (e.g. ADORA1 and A1) while others were negatively correlated in either one or both regions. In patients 5 and 6 with unconfirmed KMT2A fusions, RNA-seq revealed well known transcripts KMT2A-SEPTIN5 and KMT2A-MLLT11, respectively. It is characterised by multiple colorectal adenomas and high risk of colorectal cancer. Rosa-Perez: None. Mescheryakov: None. Background: We present a pilot study to ultimately develop a pipeline utilising in silico tools to identify and accurately infer the lengths of known and novel pathogenic repeat expansions (REs) in amyotrophic lateral sclerosis (ALS) from whole-genome sequencing (WGS) data. Santaniello: None. P17.046.A Biologically interpretable neural networks for phenotype prediction using population-cohort multi-omics data Arno van Hilten, Jeroen G. In sequencing analysis of ECM1 gene, a novel homozygous NM_004425:c.1246 C>T(p.Arg416Ter) mutation in exon 8 causing premature stop codon was detected. Thus, we diagnosed the patient with LS despite the presence of MLH1 promotor hypermethylation and BRAF V600E mutation in the cecal tumour. Nieto-Moragas: None. Chow: None. (Likely) pathogenic variants were found in 505 (17%) of cases and variants of unknown significance (VUS) in 194 (6%). Introduction: genetic predisposition to multiple sclerosis (MS) includes >200 genetic loci, with the major histocompatibility complex (MHC) region accounting for 32 independent associations. 10 bp) of ANKH were amplified by PCR and directly sequenced using Sanger method. Braat1, Liliana Ramos1, Miguel J. Orsini: None. The developed population specific low density oligonucleotide microarray can be considered as an alternative low-cost tool for heterozygous carrier screening and genetic diagnostics in republic of Sakha (Yakutia). Altogether, we suggest that AH>GH substitutions are sensitive to oxidative damage and thus can be a new marker of the redox stress in mtDNA. TBMN cases had no extrarenal manifestations, in contrast to 28% of AS cases (p = 0.01). Shaw, Cynthia L. Hinarejos: None. Taylor1 1University of Oxford, Oxford, United Kingdom, 2Institute of Molecular Biotechnology of the Austrian Academy of Sciences (IMBA), Vienna, Austria. Barreiro: None. Moreover, our region-based strategy to filter variants outperformed classical filtering strategies. Terms that are not only relevant in epilepsy and glutamatergic neurons, but are also associated with ferroptosis, which is a novel form of non-apoptotic regulated cell death attributed to severe lipid peroxidation caused by ROS production and iron overload. Grants: French Embassy in Sudan, Campus France, University of Khartoum, and the Sudan Ministry of Higher Education for the scholarship (to LE), the Wellcome Trust RDF grant (to LE), the European Union through the H2020 program (SOLVE-RD to GS), and the French ASL-HSP Association (to GS). S.C. Collins: None. A random-effect model was used to calculate the pooled odds ratio and 95% confidence interval by comprehensive meta-analysis software. Roeth: None. Results: PGT was provided free of charge to participants; their primary concern was emotional. Depending on the inclusion of different loci in the development of obesity, the nature of the relationship between the polymorphisms of these genes can change.This study was funded by the Ministry of Science and Higher Education of the Russian Federation №0852-2020-0028. One patient showed compound heterozygosity in TYR, with one frameshift and one rare missense variant. Expansion Hunter results were highly concordant with PCR-based conclusions. Celkan: None. Anomalies of CREs at distance from a gene have been identified in various genetic diseases. Introduction: Fabry nephropathy (FN) has an important impact on morbidity and mortality in Fabry disease (FD). Besides, we have shown the clinical utility of NGS based CNV-calling approach, which effectively allowed to detect of the CNV in the exome sequencing data. Acknowledgment: KP-06-N33/5 from 13.12.2019 - National Science Fund of Bulgaria S. Wagermaier: None. de Voer1, Marjolijn J. The obtained diagnostic yield (12%) is quite relevant considering the high clinical and genetic heterogeneity of PD. H.L. Weiner: B. Genetics Department, Hospital Universitario La Paz, IdiPAZ, Madrid, Spain, 8Next Generation Sequencing Section. The stages of sexual development were determined using the Tanner scale. Materials and Methods: Using deep whole genome sequencing (WGS) data from two population-based cohorts (15X WGS; N = 2,893), we carry out a protein quantitative trait locus (pQTL) analysis of 184 neurologically-relevant proteins. Gasiuniene: A. To clarify how wild type and mutant TRAF3 and NBR1 modify the effect of CYLD on NF-κB signal transduction pathway, an in vitro experimental system was set up. Zayaeva2, Marina Podolnaya1, Aleksandra Lapina1, Aliy Asanov3 1Research and Clinical Institute for Pediatrics named Academician Yuri Veltischev of the Pirogov Russian National Research Medical University of the Russian Ministry of Health, Moscow, Russian Federation, 2Russian Medical Academy of Continuous Professional Education of the Ministry of Healthcare of the Russian Federation, Moscow, Russian Federation, 3I.M. Sechenov First Moscow State Medical University, Moscow, Russian Federation. The numerous FBN1 mutations identified in MFS are located all along the gene, leading to the same pathogenic mechanism. Rickassel: None. There were no changes in the mitochondrial DNA content of patient fibroblasts. This work was supported by infrastructural projects D01-285/2019; D01-395/2020 funded by MES. W.D. Foulkes: None. Functional studies are underway to proof this hypothesis. Methods: Phenotypic and molecular data from 27 previously unreported individuals with QRICH1 variants were gathered through international collaboration and compared to those of the 10 previously reported individuals. A patient with osteosarcoma and embryonic rhabdomyosarcoma without family history had pathogenic mutation c.725G>A (rs121912655). Whole ES revealed a homozygous pathogenic variant, c.763G>A,p.(Gly255Arg), in COQ6, for which both parents were heterozygous. For comparison, we used four additional iPSC lines: one derived

from a patient with a heterozygous nonsense mutation in SHANK2 (R841X), a CRISPR/Cas9-engineered homozygous SHANK2 knockout line, and their respective isogenic controls. To date, one common risk locus for nsCPO is confirmed, and nine have been reported recently but still await independent replication. Barroso: None. Table 1: Phenotype, gene, variant and variant classification details of all 10 PGT-M cases. Beside the LEF1 activation, LEF1 gene variations were rarely observed in our cohort. Higher prevalence has been estimated in populations with Mediterranean ancestry (Armenian, Arab, Italian, Jewish, Greek and Turkish). The identified variants in ASXL1 and DNMT3A may be associated with resistance to TKI therapy and serve as prognostic markers of the TKI therapy effectiveness at the stage of CML diagnosis. P10.013.A Screening of SORD mutations in a CMT cohort expands the clinical spectrum of SORD-related neuropathy Camila Armirola-Ricaurte 1, Els de Vriendt1, Ayse Candayan2, Ognyan Asenov3, Yesim Parman4, Teodora Chamova3, Ivailo Tournev3, Esra Battaloglu2, Albena Jordanova1,5 1VIB-UAntwerp Center of Molecular Neurology, Antwerp, Belgium, 2Department of Molecular Biology and Genetics, Bogazici University, Istanbul, Turkey, 3Department of Neurology, University Hospital Alexandrovska, Medical University-Sofia, Sofia, Bulgaria, 4Department of Neurology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey, 5Molecular Medicine Center, Department of Medical Chemistry and Biochemistry, Medical University-Sofia, Sofia, Bulgaria. Employment (full or part-time); Modest; CeGaT. The interactions between the various substrates in this pathway and their competition for the pathway enzymes are currently unknown. Plazzer: None. Zarandia: None. The patient's clinic varies depending on the size and localization of the deletion. NGS performed at 4 years of age detected a heterozygous stopgain variant NM_003106.3(SOX2):c.600C>A, (chromosome 3q26.33). te Paske: None. Transactivation activity using luciferase assay, DNA-binding using EMSA, and nuclear localisation using immunofluorescence of mutated HNF1α were compared with the wild-type HNF1α and a set of positive and negative controls. P.L. De Jager: B. In fact, this SHANK2 deletion removes not only exon 16, but also a large portion of the adjacent intron. The samples were divided into two groups: "highland" (N = 80; 1900 m and more above sea level), and "lowland" (N = 90; 600-1850 m). These 50 NEMGs showed more extreme differences in expression compared to all other NEMGs, validating them as a key subset of NEMGs associated with T2D. A.M. Osman: None. Bessieres: None. It is computationally efficient and increases fine-mapping accuracy and resolution at lower cost, and is more feasible than collecting larger samples. Guerrero-Sola: None. Brishevac: None. Optic nerve damage was not present in two patients, one of whom was 16 years old. Schwaninger: None. Interestingly, HYD significantly increase OCT4 and NANOG expression by 2.5-fold and 4-fold, respectively in adult fibroblast. An antagonistic character was also established between all studied genes and combinations of combined genotypes of obesity risk in the child and adolescent population were identified. Of note, MSI score and mean frequency of unstable markers was significantly lower in CMMRD tumors when compared to sporadic MSI tumors (p = 0.002). Statistical analysis was performed by STATISTICA version 13.5.0. The result values were corrected using the Benjamini-Hochberg method. Purpose: Hereditary breast and ovarian cancer syndrome (HBOC) and Lynch syndrome (LS), the most common inherited cancer syndromes, are attributed to a single heterozygous pathogenic variant (PV) in BRCA1/2 or in a DNA MMR gene, respectively. Grigg: None. P17.064.C De novo variants within constrained coding regions are a major source of pathogenicity for rare diseases Hywel J. Dixit: None. Ranganath: None. Background/Aim: Newer approaches are required to control human cancers, natural materials derived from plants offer tremendous advantages. This burden increases as we segregate patients with other clinical symptomatology. Alhashem3, B. Materials and methods: A relational database was developed to collect variant-to-treatment mappings from systematic literature reviews (SLRs) produced by disease experts. Conclusion: The application of NGS for screening of an extended gene panel allowed us to identify the genetic cause of the disease in approximately half of the SRNS patients recruited for the study. O.V. Pachuliia: None. To ensure alignment between PCG benefits and target group needs, strong dialogical engagement of possible target groups is required, to be facilitated by PCG experts. 4/28 (14.3%) carried P, while 11/28 (39.3%) carried likely P (LP) variants. After failure to thrive and severe hypochloremic alkalosis sweat chloride (SC) was found pathologic. The analyzed parents did not carry the deletions, indicating a de novo occurrence. There are reports on PVs in other FA genes (nonNCCN-HBOC FA genes) found in cancer patients, but their association with cancer risk is not yet fully established. Early diagnose can provide the appropriate management of the case and maybe find a suitable drug among inhibitors of PI3K-AKT-MTOR pathway. Public perspectives on HGGE have often been called for and are deemed necessary for democratic decision-making about potential future applications and current proceedings. Jelovic: None. P22.026.A Specialist Medical Genetics Training Requirements Across Europe Freya Anderson 1, Ute Moog2, Peter D. Kalinkin: None. - splice junction and coverage tracks for 1 or more samples can be displayed along-side gene tracks, BAM/CRAM data, SNP or CNV callsets, normalized coverage tracks such as those generated by gCNV, and other kinds of genomic feature tracks. Bastaki: None. van Duijvenboden: None. Soares de Lima: None. Research on the basis of the collection may allow a study of the pathogenetic mechanisms of various gestational complications, and the development of new methods for their diagnosis and treatment.Funding. MicroRNA variation across time (Δmirna) was computed as the difference between baseline and follow-up microRNA measures, divided by the subject's follow-up time. There weren`t any other pathogenic or likely pathogenic variants associated with HCM. Recent reports mainly focus on structural variants encompassing the PLP1 gene, encoding the major myelin protein, responsible for a variable phenotype in females ranging from late-onset spastic paraplegia to early-onset neurological disease (Hijazi et al., Hum Mut 2020;41:150-68). A.I. Cordeiro: None. Della Monica: None. P09.093.B AGO1 amino acid changes in neurodevelopmental disorders Clarisse Delvallee, Sarah Baer, Léa Sanna, Valérie Skory, Jérémie Courraud, Nathalie Drouot, Damien Plassard, Jean-Louis Mandel, Amélie Piton IGBMC, Université de Strasbourg, Illkirch, France. Physical examination showed that growth and head circumference were on the mean curve. Ijntema: None. P09.137.B Van Maldergem syndrome 2; An extremely rare case Deniz Esin, Fahrettin Duymus, Busra Goksel Tulgar, Ebru Marzioglu Ozdemir, Tulin Cora Selcuk University, Konya, Turkey. Ware2, Stephane R. Conclusion: These findings are comparable with those from the literature and support the use of this type of genetic testing in AIS, as it helps in establishing the diagnosis of these difficult to diagnose and rare conditions. Capellá: None. Acknowledgment: BSNF, Contract NoKП-06-H33/10, 2019. Methods: Phenotypic data and diagnostic test results were collected for all children diagnosed with WT in the Netherlands (2015-2020). We have used the SYNTAX™ EDS System to produce oligos for SARS-CoV-2 LAMP, NGS and FISH assays. Ciurliene: None. Rare genetic diseases affect millions of children worldwide. All bioinformatic tools used suggested deleterious function of the protein that present the variant. Babai3, Elhami A. Conclusions: This study reports seven new polymorphisms for the IL-6 gene and its promoter region. Materials and Methods: Next generation sequencing (NGS) was performed. Accurate classification of these tumours is essential to facilitate appropriate patient management. Chinnery: None. Relative haplotype dosage is used clinically for common X-linked and recessive conditions, but is not suitable for consanguineous couples or those where there is no proband DNA available, and is too expensive to permit validation for rare disorders. Genetti10, Joseph Gonzales-Heydrich11, Parul Jayakar12, Jacob W. Their origin is not well elucidated but it seems that genetic (HOX genes) and environmental factors (maternal exposure to chemicals or stress) may be involved. However, the inclusion of novel genes in current diagnostic solutions or broader approaches, like WGS or WES, are needed for prompt and accurate diagnosis of congenital erythrocytosis. out of criteria (OOC) patients by testing criteria. Two variants of highest p-value belonged to TLR5 - rs5744168 (FDR = 0.002) and rs2072493 (FDR = 0.005). Windsor: None. Understanding the different form of CF, it is essential for early diagnosis and to achieve integral management. Materials and Methods: Fifty-one 5th year medical students participated in a vignette study covering seven uncertain prenatal ES results derived from clinical cases (e.g. incidental and secondary findings). To date, a causal relationship with the development of HCM has been established for 10 genes; for another 20 genes, there are data on individual clinical cases indicating such a relationship. Juanes1, David Gomez-Peregrina2, Daniel Perez-Gil3, Rodiel Martinez-Jimenez1, Juan M. Q.M. Janjua: None. COL9A2 mutations have been associated with AD multiple epiphyseal dysplasia, characterized by early onset of pain associated with OCD in some patients, and also with intervertebral disc disease. Ciavarella: None. While prevalence is higher in men, women shows greater psychological burden, suggesting that different coping mechanisms operate between both genders. Bichon: None. Girl also exhibits hyperactive behavior, episodes of unprovoked laughter. We performed a GWAS separately on each cohort and meta-analyzed them using a fixed-effect model. We looked at enrichment of association signal on gene-set, tissue and cell type level and examined associations with other phenotypes both at the genetic and phenotypic level. Introduction: Short tandem repeats (STRs) are repeated DNA sequences with a length of 3-6 nucleotides. SLC25A42 is the main transporter of Coenzyme A into mitochondria. Results: Colorectal tumors were molecularly subtyping as: CMS1 (10%), CMS2 (35%), CMS3 (25%), CMS4 (10%) and unknown (20%). Rodríguez-Rivera: None. Schett: None. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Modest; CRA Health LLC. P12.171.C Differences between inherited and acquired polymerase proofreading deficiencies in cancerElsa Ezquerro1, Pilar Mur1,2, Sandra García-Mulero3, Lorena Magraner-Pardo4, Rebeca Sanz-Pamplona3, Tirso Pons5, Gabriel Capellá1,2, Laura Valle 1,2 1Hereditary Cancer Program, Catalan Institute of Oncology; Oncobell Program, IDIBELL, Barcelona, Spain, 2Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain, 3Unit of Biomarkers and Susceptibility, Cancer Prevention and Control Program, Catalan Institute of Oncology; Oncobell Program, IDIBELL, Barcelona, Spain, 4Prostate Cancer Clinical Research Unit, Spanish National Cancer Research Center (CNIO), Madrid, Spain, 5Department of Immunology and Oncology, National Center for Biotechnology (CNB-CSIC), Spanish National Research Council, Madrid, Spain. The problem of uncertainty is one of the key issues for the current stage of knowledge about human genome. The aim of our study was to evaluate the combine effect of these gene variants on the clinical course of the disease. Conclusion: We report the patient with STAG1 gene variant, with Angelman-like phenotype, stereotypical hand movements and regression of skills, which is not been described before. Pelin: None. In this preliminary study we evaluate the ability of in silico tools to assess the lengths of ATXN2 CAG REs. Methods: 221 cases and 117 controls are included in this initial study. van der Zwaag: None. Conclusions: Our study showed that complex BCR-ABL1 FISH patterns were associated with worse response and progression in CML patients in Bosnia. Feliubadaló: None. Everman3, Jennifer A. Rolfs1,17, P. Higher BC/OC risk is mostly attributed to pathogenic variants (PV) in BRCA1/2 genes, as well as to PV in other high to moderate BC/OC risk genes as listed by NCCN guidelines for hereditary breast and ovarian cancer syndrome HBOC (NCCN-HBOC genes). F.J. Ramos: None. Chairta: None. Ala: None. Our findings highlight the importance of high-resolution aCGH and the critical analysis of aCGH data surrounding genes that are involved by genomic variation. Helm: None. Rolfs: None. Kolomenski5, Cecilia S. This congenital abnormality was associated with another congenital variation of the lung (0.2-1.2% of the population) which was an azygos lobe of the right lung. We therefore sought to characterise the RNA abundance profiles of three such cell lines, in order to identify genes and pathways core to this process, as well as those uniquely involved in each cell line. This syndrome is caused by mutations in the FAT4 gene. Sequencing data was analyzed through internal pipelines and included percent reads on-target, fold-80 base penalty, mean target coverage, total duplicate rate, 90th/10th percentile ratio, mean insert size. One scanning cycle of the genome for a single 7bp sequence took 30 seconds, while the gene annotations took 8 seconds. Patients are usually screened for variants in nine genes involved in erythropoiesis and oxygen homeostasis regulation, however in only 30% the genetic cause is identified. Nieves-Moreno: None. The data interpretation revealed a likely pathogenic variant - c.220G>A (p.Gly74Ser) in ACTB gene. Pasquier: B. Garcia-Linares: None. Inversions can have brutal effects by disrupting the coding sequence or more subtle impacts on gene expression. Most of the genes were involved in DNA damage repair. Methods: We recruited 15 patients who were considering predictive testing for HD from four UK regional genetics services. The HBOC genes BRCA1, BRCA2, PALB2, ATM, CHEK2, BRIP1, RAD51C, RAD51D, TP53, and PTEN, and the Lynch Syndrome genes MLH1, MSH2, and MSH6 were analyzed by commercial Hereditary Cancer Panels (Illumina) and an in-house bioinformatics pipeline. Introduction: Pseudohypoparathyroidism type 1A (PHP1A) and Pseudopseudohypoparathyroidism (PPHP) (Inactivating PTH/PTHrP Signaling Disorders type 2, IPPSD2) are two rare autosomal disorders caused by loss-of-function mutations in the imprinted GNAS gene, which encodes the α subunit of the ubiquitously-expressed G protein (Gαs). CNVs affecting miRNA gene dosage have been described to have functional influence on gene expression. De Grandis: None. W.K. Chung: None. Gene set association analysis was performed using Fisher's exact test with Plink v1.9. Case/control groups were formed accordingly: individuals with hs-CRP levels >2.5mg/l were referred as cases (N = 111), 84.74 ng/ml were referred as cases (N = 42), A;p.E518K variant, whereas no other likely pathogenic variant was identified in any other cancer susceptibility genes. Antunez: None. One female patient had a nonsense variant in the KDM6A gene. Strikingly, a previously published mouse model (Zhou et al., Hum Mol Genet 2014;23:3823-9) suggested that the developmental delay and epilepsy phenotype associated with Xq22.1 deletions could be recapitulated in female mice bearing a minimal heterozygous deletion spanning Armcx5, Gprasp1, Gprasp2 and Bhlhb9. Nikopensius: None. However, every isoform group presents by isoform unexplained Lp(a) ranges. Skory: None. As the sequencing cost (e.g., instrumentation and sequencing chemistry) decreases and the sequencing data storage and analytics capacity increases, efficient library preparation methods are becoming increasingly important for the diagnosis, prognosis and treatment of cancer. This case shows that optical genome mapping is very helpful and well suited to detect translocations and to characterize balanced translocation breakpoints. In this study, we sequenced for germline BAP1 variations 58 DNA samples archived in the Helsinki Biobank from Finnish patients with MM. p.Arg1114Gln) in RBP3 was found within the chromosome 10 locus, analyzed using our in-house databases along with open access databases and verified through Sanger sequencing. Istrate: None. Pinto Basto: None. Hellebrekers1, Ingrid P. Panuel: None. Methods: The study employed semi-structured interviews to explore the role of Islam in patients' perceptions of the cause of diagnosis, coping strategies and decision-making. Mazunin: None. The long interspersed nucleic elements (L1) utilize a "copy-and-paste" mechanism to retrotranspose their copies into new genomic loci through RNA-mediated mechanisms. R.K. Akyea: None. Gene ontology (GO) analyses and gene enrichment analyses were performed using GSEA and MsigDB. Results: The genotypes of early-stage and CRPC patients in reference to the SNPs of five genes were identified. Regrettably, causative and actionable variants cannot be found for all TRS-suspected individuals. Recurrent autosomal dominant defects were identified in HCN4, MYH7, RBM20 and TTN genes. Samples were obtained from the RAPID sample bank. Consultant/Advisory Board; Modest; Exact Sciences, Astra Zeneca. Multiple systems can be affected with highly variable phenotypic expressivity. Introduction: Citrullinemia is a rare autosomal recessive urea cycle disorder caused by argininosuccinate synthetase (ASS) deficiency. Inborn errors of metabolism account for 1.3% of affected individuals. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Modest; Biogen, Kedrion. Applying the 48-plex-panel to liquid biopsies from progressed CRC a 3-gene-signature (BOLL, DCC, SFRP2) was defined supporting patient stratification and therapy monitoring. Meitinger: None. The leading diagnostic signs are congenital absence of iris tissue, hypoplasia of fovea, accompanied by nystagmus. La Bella: None. IP8-FDMZ-2020 I. A customized skeletal dysplasia NGS panel was thus performed, and the pathogenic variant c.287_293del, p.(Cys96Phefs*19) in MMP13 gene was identified in apparent homozygosity, confirming the diagnosis of MDST. Conclusion: The systematic screening of the second term was normal in 80%. Compta: None. To improve analytical accuracy The SiMSen-seq technology was chosen (Ståhlberg et al. P09.091.D The portray of the Italian cohort of patients with variants in POGZ: new care opportunities from a deep genotyping and phenotyping Agnese Feresin 1, Beatrice Spedicati1, Giulia Pelliccione2, Corrado Romano3, Livia Garavelli4, Maria Lisa Dentici5, Nicola Specchio5, Paolo Alfieri5, Paola Grammatico6, Gabriele Trimarchi4, Margherita Baldassarri7, Alessandra Renieri7, Roberta Milone8, Flavio Faletra2, Giuseppe Cossu9, Giorgia Girotto1,2, Marco Tartaglia5, Paolo Gasparini1,2, Maria Teresa Bonati2 1University of Trieste, Trieste, Italy, 2IRCCS Burlo Garofolo, Trieste, Italy, 3I.R.C.C.S. Oasi Maria SS., Troina, Italy, 4AUSL Reggio Emilia, Reggio Emilia, Italy, 5Ospedale Pediatrico Bambino Gesù, Roma, Italy, 6Università La Sapienza, Roma, Italy, 7University of Siena, Siena, Italy, 8IRCCS Fondazione Stella Maris, Pisa, Italy, 9Centro Medico di Foniatria, Padova, Italy. Kalaycı: None. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Significant; Roche, Biogen Idec, Merck-Serono, Novartis, Teva Pharmaceutical Industries. Biesecker 1, Susan Christian2, Stephanie Cohen3, Roya Mostafavi4, Jill Slamon5, Karen E. The locus at 8p23.1 affects multiple genes that are overexpressed in appendix tissue from appendicitis patients. Furthermore, we detect chromothripsis and triploid events. Introduction and Objective: Family and twin studies demonstrate that pelvic organ prolapse (POP) is heritable, but the genetic etiology is poorly understood. Long-term monitoring with multidisciplinary management is essential for evaluating the clinical status, providing adequate genetic counseling and understanding genotype-phenotype correlation in IP. A.E. Ahmed: None. Leeuwen: None. DGE analysis enlightened the activation of severaltranscriptional pathways of induced cellular stress in fast24 compared to fed condition. Due to technical problems the method is not always informative. P03.018.B Late diagnosisof cystic fibrosisin a 59-year-old patient Elena Zhekaite 1, Elena Amelina2, Elena Kondratyeva1, Tagui Adyan1 1Research Centre for Medical Genetics, Moscow, Russian Federation, 2Scientific Research Institute of Pulmonology of the Federal Medical and Biological Agency of Russia, Moscow, Russian Federation. Lemaire-Girard: None. Performance was measured with the Ion GeneStudio S5 system, with FFPE samples and cell line controls. This patient group was chosen because the pace of decision making does not usually allow for such detailed scrutiny of this liminal space. Morgante: None. Introduction: Hydrops fetalis is a life threatening condition characterised by accumulation of fluid in a fetus' or a newborn's body compartments. Materials and Methods: Extensive literature review was conducted to collect data of pathogenic and likely pathogenic rCNVs in CAKUT patients. Ryszkowska: None. All genes are expressed in mouse growth plate. Methods. Tran Mau-Them: None. Botia2,6 1Astex Pharmaceuticals, Cambridge, United Kingdom, 2Department of Neurodegenerative Disease, Institute of Neurology, University College London, London, United Kingdom, 3NIHR Great Ormond Street Hospital Biomedical Research Centre, University College London, London, United Kingdom, 4Genetics and Genomic Medicine, Great Ormond Street Institute of Child Health, University College London, London, United Kingdom, 5Verge Genomics, South San Francisco, CA, USA, 6Department of Information and Communications Engineering, University of Murcia, Murcia, Spain. Sanchiz-Calvo: None. G.M. Repetto: None. Using summary statistics, flashfm (FLexible And SHared information Fine-Mapping) fine-maps association signals for multiple traits measured in the same sample, borrowing information between them in a Bayesian framework. The Z-score calculation using the European population database (GnomAD) showed an over-representation of particular variants in 36 of the analyzed genes. Moreover, tfap2b crispant and morphant zebrafish were generated, to determine the effect of this gene in vivo. MicroRNAs (miRNAs) are small, non-coding transcripts affecting cellular mechanisms by regulating gene expression at post-transcriptional level. We analysed 145 individuals with a CID and 70 healthy controls with ImprintSeq, a custom targeted methylation sequencing panel capable to interrogate 63 imprinting differentially methylated regions (iDMRs). P25.021.D Full-genome sequences of the first nine SARS-CoV-2 viruses from Azerbaijan AGHARZA AGHAYEV, Valeh Huseynov, Elin Aliyev, Ramin Bayramlı National Hematology and Transfusiology Center, Department of Medical Genetics, Baku, Azerbaijan. Bluefeather: None. Lasa: None. Balcells: None. Interrogation of the proximity interactome of FGFR1 mutants revealed potential treatment targets against low-grade gliomas with impaired FGFR signaling components. De Tayrac: None. Control Sanger and NGS sequencing revealed the absence p.S216L in the canonical exon 6 and confirmed the presence of p.S216L (g.38655522G>A, c.647C>T, rs201002736) in the noncanonical exon 6 of the SCN5A gene. None reported consanguinity and just 1 had inbreeding. Scheltens: None. Conclusions: Previous methods for detecting cfDNA from hCG-secreting tumours lacked sensitivity or were patient-specific, making them unsuitable for routine diagnostic testing. Materials and Methods: In our study, 75 patients (28 men and 47 women) (mean age: 49.9 ± 13.5) with multi-systemic phenotype were tested. Among triple-negative patients with pathogenic BRCA1 was 81%, with the p53 variants - 36%, with combined variants of two genes - 100% patients. Sternberg: None. This work was carried out with partial support of the RFBR grant No. 19-015-00391-A N.P. Babushkina: None. Ferreira2, Marielle Alders2, Judith J. Materials and Methods: We applied a multi-step approach for testing 277 NSHL families, which included: 1) an accurate clinical evaluation, 2) the analysis of GJB2, GJB6, and MT-RNR1, 3) the evaluation of STRC-CATSPER2 and OTOA CNVs via MLPA, 4) WES in patients negative to steps 2-3. Here, we describe 6 additional individuals from 6 families harboring protein altering variants in YIF1B, 4 of which are homozygous or compound heterozygous missense variants. Conclusions: Our series improves clinical description of WAC-related intellectual disability. Conclusions: Our study refines the phenotypic and expands the molecular spectrum of EIF3F-related syndromic neurodevelopmental disorder. P14.027.D In depth evaluation of a 9p tetrasomyMaximilian Radtke, Mareike Mertens, Susanna Schubert University of Leipzig Hospitals and Clinics Leipzig, Leipzig, Germany. We did not detect any other known pathogenic or likely pathogenic variants in other genes. P01.066.B Systematic review and meta-analysis of genetic association studies of pelvic organ prolapse John W. MLH1 protein is one component of a system of DNA mismatch repair. Yahya: None. García Peñas: None. Bel-Vialar: None. The affected individuals showed a clinically recognizable phenotype characterized by severe developmental delay, variable brain anomalies, congenital heart defects, dysmorphic facial features, and a distinctive type of synpolydactyly. Athanasiou: None. Also known low penetrance p.Glu70Lys mutation was identified in three of our VHL patients. M.L. Rice: None. Laura Roht 1,2, Hanne K. A.A. Brown: None. In addition, WGCNA of iPSCs and NPCs lines uncovered interesting co-expression modules related to ion transport (q-value = 0.0365) or glutamate receptor signaling (q-value = 0.0463), respectively. These results suggest that induction of mitochondrial biogenesis is not sufficient to improve mitochondrial respiration in MERRF cybrids and fibroblasts with high mutation load. P03.022.B Exome sequencing implicates heterozygous variant in DSTYK in functional urinary bladder disturbance Clara Vidic 1, Marcin Zaniew2, Holger Thiele3, Janine Altmüller3, Heiko Reutter1,4, Alina C. While in adults the two patients showed autosomal dominant inheritance pattern. Implementing a risk assessment tool to facilitate healthy individuals to evaluate a potential risk of familial cardiovascular disease based on their family history could serve as a solution. Recently unrelated four individuals were noted to have isolated congenital anomalies of the kidney and urinary tract (CAKUT) and hypomorphic variants in FLNA. Over 130 biobank projects have been initiated since 2015 and >94% included genomic data such as the large public-private genetic research study FinnGen. The older patient has low level of alpha mannosidase activity. This project was funded by FIS-FEDER: PI18/01476. Ateyah: None. Severe loss of function variants were lethal; surviving patients with missense variants had global developmental delay, early-onset epilepsy and arthrogryposis. The total group was characterized by an Axenfeld-Rieger anomaly, vision problems, hearing impairment, hypotonia, dysmorphic features, cardiac and brain defects (cerebellar abnormalities and ventriculomegaly). Research evidence supports the contribution of alterations in DNA methylation and genes encoding microRNAs (miRNAs) to myopia pathogenesis. Matuleviciene: None. Additionally, a three-branch extended family (315) showed linkage to a novel SLI locus at 15q24.3-25.3 (LOD = 3.06), while another family (300) showed suggestive linkage at 4q31.23-q35.2 (LOD = 2.4). Aim: To identify the underlying molecular pathology in a cohort of 55 non syndromic ARCI Egyptian families with at least one affected sib, using next generation sequencing (NGS). Posey26, James R. Zeng: None. Kluijtmans1, Udo F. Hosny3, Lina SM Fouda3, Mahmoud ER AbdelRaouf3, Amr M. In this study, we performed the largest genetic analysis of the HLA region in PD. Also in apparently non-syndromic cases a genetic diagnosis was made after testing. Mola-Caminal: None. We constructed ST- and MT-GRS for seven common diseases in the UK Biobank using a weighted (by selection index) MT-SBLUP genetic predictor. Whole exome sequencing (WES) was performed in the germline DNA from the family members and in the DNA from the tumors. Two deletions affected APC in 2/105 (2%) AP cases. Dacal: None. Introduction: Despite advances molecular diagnostic techniques such as aCGH, WES and WGS, cytogenetic chromosomal analysis still the golden standard test for detection most of the genetic abnormalities. We also detected the missense variant p.Val114Leu in one patient, which is novel, though the codon 114 is already known as a site of another missense variation, p.Val114Ala, classified as pathogenic. Whole Exome Sequencing (WES, ~19,000 genes) was implemented using Human Core Exome kit (Twist Bioscience) for library preparation and a NextSeq-500 system (Illumina) for sequencing. This variant by leading to the formation of a truncated protein, decreases Sema6b expression and stability and prevents Sema6b from reaching the plasma membrane. Employment (full or part-time); Significant; PolyOmica. This study revealed that mothers undergoing PGT require further counselling. We also performed GWAS in the same group of patients. In our study we aimed in NGS (Next generation sequencing) searching for rare /pathogenic variants in genes, connected to diabetes mellitus (DM), in Bulgarian individuals. Domarkiene: None. Inferring variant significance is complicated in ALS and FTD due to genetic heterogeneity, late age of onset, age-related penetrance and a high proportion of sporadic cases. Pathogenic variants in the TRIO gene have mainly been associated with autosomal dominant mental retardation type 44 with microcephaly and also autosomal dominant Intellectual developmental disorder type 63 with macrocephaly. We present, in the context of prenatal diagnosis, two cases with aCGH results involving a homozygous deletion that includes the CRPPA gene. Satou: None. Whether or not functional difference also plays a part in the phenotypic differences will require further research. Tõnisson: B. Spólnicka: None. FC screening is thus debated for the second family. The syndrome is almost always sporadic, and after parental analysis this deletion was shown to be de novo. To date, a total of 13 potentially spliceogenic variants were assayed and 11 of them showed aberrant splicing patterns. In order to increase diagnostic yield, we combined omic technologies to identify novel gene mutations in a cohort of 17 patients with rare undiagnosed myopathies. Funding: Solve-RD project (H2020 #779257), ERN for Neuromuscular Diseases (#870177) ERN for Rare Neurological Diseases (#739510). Fatih1, Ibrahim Hegazy2, Shalini N. We selected only those results that showed a significant reduction of expression of FYCO1. In total, 909 variants were detected in 40 genes, the most commonly mutated genes being TP53 (51.2%), KRAS (39.2%) and EGFR (17.2%). Bouschet: None. Wąsowska: None. Borggräfe: None. Di Maria: None. Material and Methods: In the presented research, 131 children with congenital heart diseases and 101 women having children with this pathology were included in the study group. Reasons for surgery were suspicion of TC (N = 3) or multinodular goitre (N = 6). For example, Russians, being one of the largest ethnic groups among the Europeans, remained significantly under-represented in GWAS for years. Recently augmentation gene treatment has been approved for patients with biallelic mutations in the RPE65 gene known to cause pigmentary retinopathy type 20 and Leber congenital amaurosis 2. Case 2: Prenatal ultrasound at 18 weeks detected shortening upper limbs compatible with phocomelia in a 29-years-old woman. Kassem: None. Unsal: None. Gerasimova: A. In addition to having impact on clinical management, this approach enables patients and their relatives to optimize individual prevention strategies. Pazoki: None. These panel detects germline and somatic mutations on FFPE samples, with sensitive and specific detection of variants down to 5% LOD. Osteogenesis Imperfecta (OI) is a well-known skeletal dysplasia. Materials and Methods: We performed massive parallel sequencing of gDNA isolated from whole blood on NextSeq (Illumina) using panel Clinical Exome (CES) kit by Sophia Genetics, followed by Sanger sequencing and CNV analysis. R.G. Boers: None. WES data were analyzed based on the prenatally observed ultrasound findings. Mitochondrial DNA (mtDNA), present in thousands of copies/cell, encodes essential polypeptides required for oxidative phosphorylation. Results: We identified 12 individuals homozygous for the c.757delG mutation. In one individual, variant of unknown significance c.1037G>A (p.Arg346His) was found. Primer concentrations in the resulting set were normalized using iROAR software. Eraslan: None. Rizzardi: None. Using clustering analysis, we were able to distinguish plasma samples acquired from BIPSS and blood plasma, indicating that the miRNA fraction characterized in this study has potentially PitNET borne origin. Case 3: fetus of pregnancy interrupted at 19+4weeks of gestational age for ultrasound findings of hydrocephalus, cerebellum hypoplasia, retrognathia, lumbar lordosis, varus feet. Methods: We analyzed methylation levels through the HumanMethylation450 Beadchip in a population of 300 (163 cases and 137 controls) subjects. Moscow experience Olesya Sagaidak 1, Alexandra Galaktionova1, Anton Olenev2, Ekaterina Kuznetsova1, Madina Kaplanova1, Maksim Belenikin1, Ekaterina Songolova3, Elena Baranova1,4 1LLC Evogen, Moscow, Russian Federation, 2Moscow City Health Department, City clinical hospital № 24, Moscow, Russian Federation, Moscow, Russian Federation, 3Moscow City Health Department, City clinical hospital № 67 named after L.A. Vorokhobova, Moscow, Russian Federation, Moscow, Russian Federation, 4Federal State Budgetary Educational Institution of Further Professional Education "Russian Medical Academy of Continuous Professional Education" of the Ministry of Healthcare of the Russian Federation, Moscow, Russian Federation. Quintanilla Mata: None. This suggests the leading role of those findings in the pathogenesis of syndromic craniosynostosis. Molecular analysis was done by PCR and reverse-hybridization in order to detect 22 of mutations most commonly associated with beta-thalassemia (Mediterranean type) and 21 of mutation covering >90% of α-globin defect. Deveaux: None. We determined the minor allele frequency (MAF) using gnomAD (MAF 26, which means a small viral amount in the analysed samples. In the 1000G data, carrier frequency was ≈0.024 and ≈0.019 in Europeans and South-Asians, with no carriers in Africans and East-Asians. MicroRNAs (miRNAs) packaged into exosomes function as paracrine effectors in cell communication and the kidney is not exempt. Jiang: None. This case highlights the association of severe congenital genitourinary malformations with EEC3 syndrome, a feature not described in other TP63-related pathologies. This work was supported by DST-SERB grant (EEQ/2019/000477), CSIR-SRF grant (09/1165(0010)/2019-EMR-I), TIFAC and DST-FIST. Shawky: None. We have confirmed the pathogenicity of four novel HNF1A variants located in the region encoding HNF1α-DBD domain using functional studies. Methods: We performed a trans-ancestry meta-analysis of genome-wide association studies (15) imputed with 1000G / HRC reference panels, comprising 118,780 individuals (81.3% European, 10.7% Hispanic and 7% African). Clinical case Iryna Lastivka 1, Vita Antsupova2, Ljudmila Brisevac3, Larysa Sheiko3, Iana Ushko2, Volodymyr Davydiuk4 1Bukovinian State Medical University, Chernivtsi, Ukraine, 2Bohomolets National Medical University, Kyiv, Ukraine, 3Shupyk National Medical Academy of Postgraduate Education, Kyiv, Ukraine, 4National Pirogov Memorial Medical University, Vinnitsa, Ukraine. Variants were evaluated regarding pathogenicity using bioinformatic filtration and manual variant classification. The genetic etiology of intellectual disability remains elusive in almost half of all affected individuals. A Bonferroni adjustment was applied correcting for the number of tested CNVs to declare significance (p 98%HetSNP sensitivity with 109Gb sequenced across inputs (100-500ng). Anatomical distribution referred of osteochondroma was mainly in long-bone extremities (65.2%) and hands (43.5%), nevertheless genotype-phenotype correlation by genes was not observed; in 7 patients (30.4%) osseous deformities required surgery but malignant degeneration was not notified. Sukarova-Angelovska, D. MIUR "Dipartimenti di Eccellenza 2018-2020". In view of the increase in diagnosis of URD, it seems fundamental to establish them as a research subject and to study the ethical issues surrounding the announcement and accompaniment of such diagnostic results. Muntoni: B. 10q26 deletion syndrome (OMIM #609625) is a rare autosomal dominant genetic disorder with about 100 patients reported. LASSO logistic regression was used for extracting relevant genes. Bilgin1, Ahmet Sayıcı1, Fatih Coşkun1, Furkan M. Meyer Children's Hospital, Firenze, Italy. Khatib: None. Conclusions: Our results demonstrate the value of data repositories, which combine clinical and genetic data, for discovering and confirming gene-disease associations. Background: Here we present journALS, a web-application designed to assess the clinical significance of all previously reported amyotrophic lateral sclerosis (ALS)- and frontotemporal dementia (FTD)-associated genetic variants. Grants: ISCIII co-funded with ERDF funds [PI18/00147], the Fundació La Marató TV3 [20143130-31], Generalitat Valenciana [PROMETEO/2018/135]. Szalkowska: None. C.D.A.C. Quaio: A. The ATXN2 CAG-repeat length was determined by PCR followed by polyacrylamide gel electrophoresis, while the SNP rs7969300 was assessed by qPCR using a TaqMan assay. Hsueh: None. In summary, the phenotypes of the two children reported here fit well with the features of the recently reported BICRA-based NDD such as developmental delays, microcephaly, short stature and genitourinary and cardiac abnormalities. Results: clinical and genetic features of mtDNA polymorphism carriers were characterized by multiple organisms, clinical polymorphisms, predominant involvement of energotropic organs. Loizidou2,3, Kristia Yiangou2,3, Andrea N. Materials and Methods: Macrodissected FFPE samples of cutaneous melanoma samples, benign nevi and skin controls were analyzed using a genome-wide DNA methylation array. Aouichaoui: None. We identified several novel genes for DBD broadly, in addition to numerous candidate genes for MEG, MIC, MCD and other DBD. Smirnova3, Olga G. SNVs were introduced into expression plasmids by site-directed mutagenesis. We also assessed HNF1A and HNF4A variants (well-established causes of MODY) and conducted multiple sensitivity analysis (different control cohorts, synonymous variant enrichment) to validate our results. P12.021.A The clinical significance of combined effect in BRCA1 and p53 genes variants on breast cancer treatment course Olha Lobanova 1, Z Rossokha2, V Cheshuk1, N Medvedieva2, R Vereshchako1, N Gorovenko3 1National Medical University Bogomolets, Kyiv, Ukraine, 2State Institution Reference-centre for Molecular Diagnostic of Public Health Ministry of Ukraine, Kyiv, Ukraine, 3Shupyk National Medical Academy of Postgraduate Education, Kyiv, Ukraine. Both the proband and his sister are indeed affected by recurrent oral candidiasis, hypothyroidism, type 1 diabetes mellitus and Addison disease. Conclusions: Comparison of aberrant expression of ncRNAs participating in epigenetic regulation with clinical characteristics will allow to evaluate their diagnostic and prognostic potential in gastric cancer. Results: 31/33 countries recognise a specialty called "Clinical", "Medical" or "Human" Genetics. Toussaint: None. ALS is a fatal neurodegenerative disorder which causes the death of neurons controlling voluntary muscles. P12.049.A Analysis of genomic complexity in patients with chronic lymphocytic leukemia (CLL) using optical genome mapping Anna Puiggros 1,2, Silvia Ramos-Campoy1,2, Tuomo Mantere3, Marta Salido1,2, Carme Melero1,2, María Rodríguez-Rivera1,2, Sandrine Bougeon4, Rosa Collado5, Mireia de la Rosa1,2, Eva Gimeno6,7, Rocío García-Serra5,8, Sara Alonso9, Marco Moro9, María Dolores García-Malo10, Jacqueline Schoumans4, Alexander Hoischen3,11, Blanca Espinet1,2 1Molecular Cytogenetics Laboratory, Pathology Department, Hospital del Mar, Barcelona, Spain, 2Translational Research on Hematological Neoplasms Group, Cancer Research Program, Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Barcelona, Spain, 3Department of Human Genetics, Radboud University Medical Center, Nijmegen, Netherlands, 4Oncogenomic laboratory, Hematology service, Lausanne University Hospital, Lausanne, Switzerland, 5Department of Hematology, Consorcio Hospital General Universitario, Valencia, Spain, 6Department of Hematology, Hospital del Mar, Barcelona, Spain, 7Applied Clinical Research in Hematological Malignances, Cancer Research Program, Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Barcelona, Spain, 8Research Foundation from Hospital General Universitario, Valencia, Spain, 9Department of Hematology, Hospital Universitario Central de Asturias, Oviedo, Spain, 1010 Department of Hematology, Hospital Universitario Morales Meseguer, Murcia, Spain, 11Radboud University Medical Center Center for Infectious Diseases (RCI), Department of Internal Medicine and Radboud Institute for Molecular Life Sciences, Radboud University Medical Center, Nijmegen, Netherlands. The latter were either regions with no clear disease association [70% (45/64)], or susceptibility loci with low penetrance (cut-off set at 20%)[30%(19/64)]. Subgroup Sample size (%) Adjusted R2 (%) Adjusted R2 (proportion of the whole sample) Whole sample 295,189 (100) 0.92 1 Alcohol consumption mean ± 1 SD 204,384 (69) 0.45 0.49 Alcohol consumption mean ± 2 SD 278,689 (94) 0.89 0.97 Alcohol consumption quintile 1 59,025 (20) 0.004 - Alcohol consumption quintile 2 59,196 (20) 0.037 - Alcohol consumption quintile 3 61,121 (20.7) 0.00 - Alcohol consumption quintile 4 56,428 (19.1) 0.03 - Alcohol consumption quintile 5 59,419 (20.1) 0.15 - Men 134,169 (45) 1.29 - Women 161,020 (55) 1.07 - Age group 1(38-52) 97,698 (33) 1.05 - Age group 2 (53-60) 89,294 (30) 0.94 - Age group 3 (61-72) 108,197 (37) 0.79 - X. It is associated with pathogenic variations in WDR45 almost exclusively in females due to probable male lethality. Lui3, Katrin Hinderhofer1, Jeffrey Baron3, Jan M. Another patient had a potentially sensitive mutation to anti-EGFR therapy KRAS A59T along with the PIK3CA mutation E545K. Kaakinen: None. His483Arg, p. The Cys316 minor allele was associated with a 0.4 % higher body fat percentage and 0.5% higher trunk fat percentage. Sousa1, Renan Reis2 1UNIFENAS, Alfenas/MG, Brazil, 2UNIVAS, Pouso Alegre/MG, Brazil. Yaylacioglu Tuncay: None. Furthermore, PINK1, a PD-related gene, represses pro-inflammatory cytokine production mediated by the cGAS/STING pathway (an innate immune signaling pathway that detects cytosolic DNA). The full process of DNA isolation, labeling, data collection, and SV calling takes four days total turn-around-time. The most common rearrangement of the LDLR gene in the CR is a duplication of exons 2-6 (exon2_6dup), which is also the sixth most common LDLR mutation in the CR. P09.112.A Correlation of GAA genotypes and enzymatic activity of acid-α-glucosidase among Hungarian Pompe disease patients Aniko Gal 1, Zoltan Grosz1, Beata Borsos1, Ildiko Szatmari2, Agnes Sebok3, Laszlo Javor4, Veronika Harmat5, Katalin Szakszon6, Livia Dezsi7, Eniko Balku8, Zita Jobbagy9, Agnes Herczegfalvi10, Zsuzsanna Almassy11, Levente Kerenyi12, Maria Judit Molnar1 1Institute of Genomic Medicine and Rare Disorders, Semmelweis University, Budapest, Hungary, 2First Department of Pediatrics, Semmelweis University, Budapest, Hungary, 3Department of Neurology, University of Pecs, Pecs, Hungary, 4Petz Aladár County Hospital, Győr, Hungary, 5Department of Pediatrics, St. Rafael Hospital of Zala County, Zalaegerszeg, Hungary, 6Department of Pediatrics, Faculty of Medicine, University of Debrecen, Debrecen, Hungary, 7Department of Neurology, University of Szeged, Szeged, Hungary, 8Department of Pediatrics, Andras Josa Teaching Hospital, Nyíregyháza, Hungary, 9Department of Neurology, Bács-Kiskun County Hospital, Kecskemet, Hungary, 10II. OGM allowed the interpretation of complex rearrangements or provided additional structural information to CMA in 11/22 (50%) patients. In patients with Familial Hypercholesterolemia (FH), increases in Lp(a) and homocysteine levels could contribute to the cumulative burden of risk factors for atherosclerotic-cardiovascular disease2. Whenever possible, the extension of mosaicism within the different embryonic layers was examined. John: None. O.I. Zhdanovych: None. In this reading, these instruments are complementary to each-other and can establish as such a special product liability regime applicable to IVDR products. The TLR7/TLR8 locus was associated with disease onset before and the SH2B3/ATXN2, ITGA4/UBE2E3 and IL2/IL21 loci after 7 years of age. Hoefele: None. We applied whole exome sequencing (WES) and co-segregation analysis on DNA samples from all available individuals which revealed a novel recessive biallelic mutation (NM_015978.2: c.1531T>C: p.S511P) in the highly conserved kinase domain in cardiac troponin I-interacting kinase (TNNI3K) gene. Vasilev: None. On the other hand, somatic POLE exonuclease domain mutations are identified in 7-15% of endometrial cancers, 0.5-8% of colorectal cancers, and more rarely in other tumors. DNA libraries were prepared following Oxford Nanopore protocol and sequenced on the GridION device for 48 h. B. Methods: 809 pharmacogenetic alleles, distributed through 19 genes, defined in a Clinical Pharmacogenetics Implementation Consortium guideline were interrogated in 5,001 individuals with a standard diagnostic WES testing (57% Spain; 27% Colombia; 11% Brazil; 5% other). As a proxy of cellular biology, extracellular vesicles (EVs) are useful for studying cellular regulation of complex phenotypes. Tetracycline resistance was associated with tetA (n = 5) and tetB (n = 3). Gheorghe: None. Rački: None. E.V. Zhukovskaya: None. Levitskaya2, Elena A. Clinically at age 17, he had short stature (160 cm; -2.5 SD) and a triangular face with severe maxillary prognathism. Materials and Methods: A cohort of 69 patients and age- and sex-matched control group were enrolled. Clinical and molecular characterization of patients with NS. Monsma: None. Arrigoni: None. P04.055.D Sixth family with confirmed metaphyseal dysplasia, Spahr type and a novel variant in MMP13: case report and review of the literature André M. Publicly-available transcriptomic and epigenomic datasets were analyzed and the 'Activity-by-Contact' (ABC) method for scoring enhancer elements and linking them to target genes was used. Introduction: AGO1 is a RNA-binding protein (RBP) from the Argonaute family involved in gene-silencing mediated by small non-coding RNA and additional processes regulating gene expression. Ormieres: None. Comparing sleep and epilepsy aspects for these 6 conditions reveal major differences. Pras: None. Evrony1,5 1Center for Human Genetics and Genomics, New York, NY, USA, 2Division of Clincal Genetic Services, Department of Pediatrics, New York, NY, USA, 3Nordic Biosciences Biomarkers and Research, Harlev, Denmark, 4Division of Molecular Medicine and Gene Therapy, Lund University, Lund, Sweden, 5Department of Pediatrics, and Department of Neuroscience & Physiology, New York University Grossman School of Medicine, New York, NY, USA. H.Y. Leong: None. P03.005.A Systematic variant reinterpretation in patients with type-IV-collagen-related nephropathy (Alport syndrome/thin basement membrane nephropathy) reveals a high rate of ambiguous resultsKorbinian M. This locus includes GJB2 and GJB6 genes that express connexins at the cochlea. Results: GRS was associated with alcohol consumption (0.122; 95% CI = 0.117-0.126) within the UKB. Donadio, Milton Barros, Karina M. Conclusions: We believe the haploinsufficiency of both genes SATB2 and CTLA4, by 2q32q33.3 microdeletion, might explain the phenotype of these patients. 18-29-14073. Enchondromas are benign cartilaginous tumors, typically localized in the metaphyses. R.S. van der Post: None. Hofstra, Marieke F. van den Roek: None. Kovanda: None. P04.066.C A family with Osteochondritis Dissecans and multiple fractures harboring COL9A2 and PLS3 Mutations Estelle Arnaud Gouttenoire 1, Sophie Lang-Andrey2, Françoise Lemaire-Girard1, Jean Dudler2, Michael Morris1 1SYNLAB Switzerland, Department of Genetics, Lausanne, Switzerland, 2HFR Fribourg, Department of Rheumatology, Fribourg, Switzerland. A.D.C. Paulussen: None. Introduction: Cervical cancer ranks as the fourth most common cancer in women worldwide. Multivariable MR was used to evaluate and quantify the mediating role of the risk factors in the relationship between BMI and endometrial cancer risk. Introduction: The prevalence of ichthyosis vulgaris (IV) in Eastern Ukraine is 1:2557. SVInterpreter corroborated the previous classification in about 84% of the SVs. In about 5% of the SVs, SVInterpreter gave indication of possible position effect, through phenotype similarity, disrupted chromatin loops or genome wide association studies. Thus, the aim of this project is to perform a deep phenotyping of the current cases and review all cases in which a pathogenic variant has been found in RNF125. We propose the name "TAB2-related syndrome". Ramensky: None. P20.038.A Mitochondrial D-loop region methylation and copy number are not altered in peripheral blood of Parkinson's disease patients Andrea Stoccoro 1, Adam R. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Modest; qGenomics. The aim of the research was to identify novel DSD genetic variants using whole exome sequencing (WES). Considering the unmet medical needs for most life-longing NDDs and recent evidences on the improvement of behavioural impairments in POGZ knock-in mice, we propose new care perspectives through the inhibition of glutamatergic signal and the mitigation of excitatory neurons. Previously, we reported 3 patients from 3 unrelated families with monoallelic missense variants and 8 patients from 5 unrelated families with biallelic variants in PLXNA1 (unpublished). Methods & Results: A hospital based case-control study was carried out in Tanzanian population(263 BC patients and 250 controls matched for sex and age). Thus, with the aim of providing a strategy with these characteristics arises our NGS-COVID test, a NGS based methodology that allows differential variant diagnosis with a similar cost to PCR assays. We report a homozygous p.(R222S) substitution in HSP47 in a child with severe osteogenesis imperfecta (OI). A.C. Tutulan-Cunita: None. Results: 117 participants (60 HCPs and 57 relatives) generally valued the DeSIRe for improving understanding of β-TM, thalassaemia carriers and genetic inheritance. Z.A. Azher: None. P22.011.B New Spanish translation of EuroGEMS.org: the ESHG's guide to international educational online resourcesAdam P. Blume, Marwin Ko, Ryan W. A significant driver of this growth is Next-Generation Sequencing (NGS), a modern DNA sequencing technology instrumental in achieving complete DNA sequences or genomes of humans, many animals, plants, and microbial species. S.S. Nayak: None. Yurteri: None. Naja: None. The conventional genetic exon-focused approaches fails in about 1% of haemophilia B patients. Indranath: None. Amelina2 1Rostov State Medical University, Rostov-on-Don, Russian Federation, 2Southern Federal University, Rostov-on-Don, Russian Federation. Lemos: None. Verloes: None. Pathogenic rCNVs of seventeen patients, located on 7 chromosomes, contained at least one miR-548 member. Aposteanu: None. Patients and Methods: A 17-year old girl with the phenotype of facioscapulohumeral muscular dystrophy experienced the onset of her symptoms in the neonatal period. The other sSMC was characterized by subcen-MFISH. Depending on the inherited or somatic nature of the variant, one residue may be mutated to generate one or other amino acid. Novelletto: None. We achieved an AUC of 0.98 in the held-out test set for smoking status (current smoker vs never smoked) and identified well-replicated genes such as AHRR, GPR15 and LRRN3. 1) The results were displayed in a text file which limited the annotations which that could be displayed. Sá: None. Deindl: None. L.E. Sanderson: None. De novo variants represented 56.5% cases versus 44.5% inherited. During the treatment, 66 patients (mean age ± SD 63.5 ± 8.03 years) were prescribed insulin preparations and 87 patients (65.55 ± 8.27 years) were observed without insulin. Results: Based on the receiver operator curves the five best performing tools for each dataset were determined. Harrison2, Ali Reza Tavasoli3, Navid Almadani4, Robert S. Methods: Each variant was mapped in the crystal structure of HINT1 and in silico folding stability predictions were performed. Introduction: Recently we demonstrated the potential for new therapeutics to extend female reproductive lifespan by manipulating DNA damage response (DDR) pathways (MedRxiv . Avraham: None. Significant differences in PPi levels between D+M and N+M genotypes were found in bulk analysis only (P T, (p.Arg227Ter) Nonsense Heterozygous rs121434248 / CM920642 AR Pathogenic c.344G>A, (p.Gly115Asp) Missense Heterozygous rs121434246 / CM920633 AR Probably Pathogenic SRD5A2 codifies to 5-alpha-reductase type 2. Sergushichev: None. When available parents were studied, a maternal origin was observed in four patients and paternal origin in one.Attending the phenotypic variability of the patients, even with similar genomic regions involved, a better clinical characterization is important particularly in duplications sharing a smaller subset of genes. Amigo: None. Finally, we used mediation analysis to characterise the indirect effect of BMI via the mediators. Fernandez-Tajes: None. Materials And Methods: Over the last year, our working group identified and implemented the clinical and laboratory needs to achieve a genetic diagnosis through rWES. This project is supported by the Generalitat de Cataluña through an Industrial PhD grant. P08.018.D Novel variant in DDX3X causes syndromic DDX3X related neurodevelopmental disorder Kamilė Šiaurytė 1, Kristina Grigalionienė2,3, Algirdas Utkus2, Aušra Matulevičienė2 1Vilnius University, Vilnius, Lithuania, 2Department of Human and Medical Genetics, Institute of Biomedical Sciences, Faculty of Medicine, Vilnius University, Vilnius, Lithuania, 3Centre for Medical Genetics at Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania. Introduction: We report a multi-generational family of several individuals with cutis laxa, bowel perforation, cardiac rupture and clinical diagnosis of Ehlers-Danlos syndrome. Here, we describe the prenatal and autopsy findings of a male fetus with lethal complex malformations due to a hemizygous deletion Xq26.2-q26.3. Methods and Results: Routine first trimester screening detected several abnormalities (nuchal edema, ascites, dextroversio cordis, exomphalos, growth retardation) which prompted molecular karyotyping. Introduction: Ets variant gene 5 (ETV5), belongs to a family of transcription factors, regulates several genes essential for spermatogonial stem cells (SSCs) self-renewal. Objective: Array comparative genomic hybridization (CGH) is nowadays the best tool to identify chromosomal abnormalities. We then tested if the FMR1 allelic score obtained correlates with XCI pattern in females with idiopathic infertility. Arán: None. Results: The resulting gene co-expression modules were annotated using the WGCNA R package and gprofiler2 to identify modules enriched for cell type-specific markers and biological functions of interest as defined by the Gene Ontology and KEGG databases. Telomeres are complexes of short tandem DNA repeats and proteins at the ends of chromosomes. Loss-of-function variants in the SCN4A gene are the cause of autosomal recessive (AR) severe foetal hypokinesia and congenital myopathy. RT-PCR showed that the c.651-1G>C variant causes an in-frame deletion of 32 amino acids (p.Phe218_Lys249del). Eismont: None. An additional goal is to analyze selected CpGs associated with particular habits in terms of their correlation with aging processes and then validate them as markers for lifestyle-induced diseases. P09.097.B Don't take your (virtual) panels for granted! Fulvio D'Abrusco 1, Valentina Serpieri1,2, Romina Romaniello3, Filippo Arrigoni4, Roberto Ciccone1, Renato Borgatti5,6, Enza Maria Valente1,2 1Dept. Aim and method: Our aim was to understand the opportunities for personalisation and how new knowledge from breast cancer prevention research could best be integrated into personalised prevention pathways.We reviewed the scientific and policy literature to gain an understanding of the present. Less than 30% of cases of hereditary sensorineural hearing loss in Ossetians were GJB2-associated. Herranz Pérez: None. Present study shows that gene-dosage anomalies represent a significant proportion (approximately 15%) of the EVC/EVC2 mutation spectrum. Additionally, we used a siRNA strategy to knock-down TRAF7 in control fibroblasts and analysed the expression of selected genes by qPCR. While these innovations offer exciting new opportunities and can empower families with increased knowledge about their reproductive risks and with decision-making autonomy, they have to be carefully introduced in an evidence-based and ethically responsible manner and monitored after implementation. Introduction: Mitochondriopathies constitute a clinically important subgroup of (neuro-)pediatric disorders. F.T.M. Them: None. Introduction: Down syndrome (DS) is caused by the presence of an extra copy of full or partial human chromosome 21. A.A. Nazarenko: None. In order to search for a molecular genetic cause of disease in patients we carried out the exome sequencing using the TruSight Inherited Disease panel (Illumina, USA). S.M. Morgan: None. Constitutional MMR deficiency (CMMRD), caused by germline bi-allelic PVs affecting one of four MMR genes, results in a high propensity for hematological, brain, intestinal tract, and other malignancies in childhood. Plank: None. 3: %-increased in variance explained from single-trait to multi-trait GRS. The RNF123 locus was replicated (meta-analysis p = 0.0002), the ATP2C1 locus showed suggestive association (p = 0.0227), and the COMT locus was not replicated. Daga: None. The template contents adhered to existing guidelines and was structured so that, even for very complex results, the most important information was on the first page. Mascia: None. Tobias University of Bristol, Bristol, United Kingdom. P06.037.B Prevalence and clinical prediction of mitochondrial disorders in a large neuropediatric cohort Amelie T. Sironi: None. F.G.L. Mundim: None. CCHS is characterized by a predominant respiratory phenotype due to sudden hypoxic manifestation, a condition resembling two other unexplained perinatal disorders caused by defective ANS, apparent life-threatening event (ALTE) and Sudden and Unexpected Infant Death (SUID), among which the vast majority is represented by Sudden Infant Death Syndrome (SIDS). Methylation marker levels were correlated with baseline tumour volume and treatment response and compared with the standard tumour markers CEA and CA 19-9. S.M. El-sadig: None. Kogelman1, Madeline Ernest2, Katrine Falkenberg1, Gianluca Mazzoni3, Julie Courraud2, Li Peng2, Susan Svane Laursen2, Arieh Cohen2, Jes Olesen1, Thomas Folkmann Hansen 1 1Copenhagen University Hosital, Glostrup, Denmark, 2Statens Serum Institut, Copenhagen, Denmark, 3Copenhagen University, Copenhagen, Denmark. However, due to multiple testing constraints GWAS associations must exceed a stringent "genome-wide significance threshold" in order to be considered robust. A.M. Smirnova: None. It has been important to prioritize certain analyses, particularly those of "actionable" genes in diagnostic situations, involving specific treatment and/or management. Erdogan: None. It is a good alternative to amplicon sequencing as it has greater discovery potential at the same level of cost-effectiveness. Employment (full or part-time); Significant; Blueprint Genetics Inc. We then established the NgIgG regulatory network and attempted to estimate the lower boundary of the proportion of heritability that can be accounted for by the trans-regulation of the core pathway. M.L. Martinez-Fierro: A. P. This sequence change creates a premature translational stop signal NP_003097.1:p.(Tyr200Ter), classified as pathogenic. Zivotic: None. Di Nanni: None. Acute myeloid leukemia (AML) with 11q23 rearrangement causing fusion of the KMT2A gene with various specific partner genes (AML-KMT2A-r), is one of the most common subtypes of pediatric AML (~18%). Anastasovska1, E. Experts call ethical limitations and responsibility to patients the main principles of their work. Potter: None. Another notable finding is the severity of the diaphragm defect: diaphragmatic hernia is frequent in SGBS1 but agenesis of the diaphragm has not been previously reported. Strokova: None. A revised approach to the provision of genetic testing services is required to ensure equitable access, empower patients, improve access to clinical trials, therapy and delivery of care.Funded by an educational grant from the Allergan Foundation. Nitzan: None. This information may help in managing patients with SIDDT. The second one is described in literature in a patient presenting CMT2A. The alterations in expression level of some transcripts (mRNAs and miRNAs) were investigated by qRT-PCR and immunofluorescence. Variants were identified at 33 different loci; SPAST (n = 89 cases) and SPG11 (n = 25) were the most frequently involved. The affected genes -- PALB2, ATM, MSH2 and PMS2 -- are not known to be high prostate cancer risk genes. Estimating heritability and genetic correlation is of essential importance for understanding the genetic architecture of complex traits. S.M. May-Wilson: None. The molecular diagnostic yield was 13.7% overall (n = 1485; 102 genes) and 0.18% for TPP1 (n = 20). Pietro Formisano: None. The purpose of our studies is to establish the composition of the regions of the genome over 3 or 5 Mb which can be in variable copy number without phenotypic consequence. Cannizzaro: None. P.W. Kristensen: None. Klyosova: B. We analyzed a total of 36 samples by targeted RNA sequencing. P12.103.C Genetic causes of sarcomas development in young patients Nathalia de Angelis de Carvalho, Karina Miranda Santiago, Joyce Maria Lisboa Maia, Maria Nirvana da Cruz Formiga, Diogo Cordeiro de Queiroz Soares, Daniele Paixão Pereira, Felipe D'Almeida Costa, Dirce Maria Carraro, Giovana Tardin Torrezan AC Camargo Cancer Center, Sao Paulo, Brazil. Ersoy Tunali: None. Hilger1,5 1Institute of Human Genetics, University of Bonn, Bonn, Germany, 2Department of Pediatrics, University of Zielona Góra, Zielona Góra, Poland, 3Cologne Center for Genomics, University of Cologne, Cologne, Germany, 4Department of Neonatology and Pediatric Intensive Care, Children's Hospital, University of Bonn, Bonn, Germany, 5Department of Pediatrics, Children's Hospital, University of Bonn, Bonn, Germany. This study was supported by INSF (Iran National Science Foundation) with grant number 960111200 to Kimia Kahrizi. Friedrich: None. P.M. Krawitz: None. Mean time to reporting was 11 calendar days (range 6-26 days). Pappaert: None. HR-mediated DSB repair requires the ATM-dependent generation of 3' single-stranded DNA (ssDNA) via CtIP-mediated DNA end resection. Klink: None. Bolasell: None. J.J.M.W. van den Heuvel: None. Introduction: The publication of the UK British Society for Genetics Medicine (BSGM) consent and confidentiality guidance in 2019 highlighted the need and desire for separate and more detailed considerations of the ethical issues in two areas: genetic testing in childhood, and prenatal genetic testing. Rooij, Wiro J. Barakat1, Tjakko van Ham1, Namik Kaya3 1Erasmus University Medical Center, Dept of Clinical Genetics, Rotterdam, Netherlands, 2King Faisal Specialist Hospital & Research Center (KFSHRC), Dept. Broccoli: None. We report a case of recurrence of COFS3 syndrome within the same family, with similar diagnostic features. 928(42%) by Tele-counseling. Introduction: Sickle cell disease (SCD) is the most common single-gene indication for prenatal diagnosis in England. Introduction: Familial Mediterranean Fever (FMF) is an autosomal recessive hereditary disorder caused by mutation in MEFV gene. Introduction: Next Generation Sequencing (NGS) in cardiomyopathies has improved the diagnostic yield. We compared these rates to expected ARCs rates in first-cousin couples. Methods: We performed clinical whole exome sequencing, with analysis of a 189 gene panel associated with hearing loss, in a prospective cohort of 70 patients including 61 children and 9 adults presenting with hearing loss from 2017 to 2020. The protein product of this gene (TGFBIp) was shown in the cornea of zebrafish. NCL is the most common childhood neurodegenerative disease with a prevalence of 1:1000000 to 1:14000 worldwide. Sun: None. However, a detailed postnatal examination was not possible. Neri: None. The Treatabolome DB schema is based on data submission and allows discoverability of information from the SLRs. Treatabolome DB will be publicly accessible through programmatic interfaces and a web portal supporting queries of terms including diagnostic (ORDO, OMIM, and HPO), gene, variant, and treatment (ChEBI, UMLS or MeSH). Gouy: None. Zaidel-Bar: None. Kekou: None. The NPHP4 gene is expressed in connecting cilium, which normally performs important function of trafficking between the external and internal segments of photoreceptors. Baudry: None. Rappold 1 1Institute of Human Genetics, Heidelberg, Germany, 2Leiden University Medical Center, Leiden, Netherlands, 3National Institute of health, Bethesda, MD, USA. Additional features included strabismus, cryptorchidism, joint hypermobility, and abnormal foot position. It consists of a CNV, resulting in >40 protein isoforms. Fenz Araujo: None. Zayed: None. This variant neither found in ExAC nor 1000G databases. J.S. Cohen: None. Vollenweider: None. Tuncali: None. Results: The sensitivity of detecting a germline mutation in FFPE DNA tissue was 92%. Results: High resolution chromosome analysis revealed a reciprocal translocation between chromosomes 4 and 12 with ISCN formula: 46,XY,t(4;12)(q33;q22). M.B. Zhilova: None. CNVs contributed to the diagnosis of 17.1% patients; 64.3% of CNVs were intragenic. A.M.A. Babai: None. A.S. Khan: None. Western blotting identified a stable truncated mutant PTRHD1 protein expressed in the lymphocytes cells obtained from the peripheral blood of the patients. Using comprehensive genetic testing, which simultaneously examine genes associated with different types of dementia could be a feasible and cost effective way to include in the diagnostic workup. Further, a retrospective analysis of previously published cases with >=2 disease loci (N = 69) revealed that those cases display significantly increased F values (0.062 vs. Poli: None. Conclusion: We present a case report of successful molecular genetic diagnosis of rare CMD, that shows the important role of X-ray diagnosis in targeted molecular genetic diagnosis of skeletal dysplasia. RNA studies demonstrated the complete absence of ERGIC1 expression in the two affected siblings and a nearly 50% decrease in the heterozygous parents. Results: 14 polyposis-associated genes were analyzed in 26 colorectal samples by high-coverage sequencing. P02.064.A Whole locus sequencing identifies a prevalent founder deep intronic RPGRIP1 pathologic variant in the French Leber congenital amaurosis cohort Isabelle Perrault 1, Sylvain Hanein2, Xavier Gérard1, Nelson Mounguengue1, Ryme Bouyakoub1, Mohammed Zarhate3, Cécile Fourrage4, Fabienne Jabot-Hanin4, Béatrice Bocquet5, Isabelle Meunier5, Xavier Zanlonghi6, Josseline Kaplan1, Jean-Michel Rozet1 1Laboratory of Genetics in Ophthalmology (LGO), INSERM UMR1163, Institute of Genetic Diseases, Imagine and Paris Descartes University, Paris, France, 2Translational Genetics, Institute of Genetic Diseases, Imagine and Paris Descartes University, INSERM UMR1163, PARIS, France, 3Genomics Platform, Institute of Genetic Diseases, Imagine and Paris Descartes University, Paris, France, 4Bioinformatic Platform. Only one patient was homozygous for IVS 1.6[T>C]. Non-obstructive diffuse coronary artery disease (CAD) was also observed. The role of this gene is to regulate the activity of the mitochondrial multienzyme pyruvate dehydrogenases complex (PDC). NGS and MLPA tested negative. It was confirmed increased expression levels of miR-21-3p and miR-210-3p, respectively 78.94% and 39.47%. Souto: None. Parents are carriers of this deletion. To date, no genome-wide association study (GWAS) has been conducted for sepsis susceptibility. Schrappe: None. We report more de novo variants (37) than inherited ones (14). For 3 of them (FRA10AC1, RFC1, HK1) the result was not replicated. Methods: Rare genetic variants in 36 genes encoded proteins related to pathways involved were analyzed by NGS in 12 patients with FV during AMI. Introduction: The hemifacial microsomia (HMF) is a heterogeneous genetic disorder affecting the development of the structures derived from the first and second branchial arches such the jaw, the buccal structures and the hearing system. Conclusions: SARS-CoV-2 whole-genome sequencing is a highly feasible and powerful approach for tracking virus transmission. Genetic studies in adult cohorts found multiple markers associated with HGS and showed genetic correlation with bone density traits. Elgoyhen1, Viviana K. Siccha: None. Petkova: None. P03.038.B Effects of growth hormone treatment in Noonan syndrome: correlations with genotype Diana Miclea 1,2, Yline Capri2, Alain Verloes2 1"Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Cluj-Napoca, Romania, 2Department of Genetics, APHP- Robert Debré University Hospital, Paris, France. Fiorentini: None. Zazo: None. Cederroth9,2,7, Jose Antonio Lopez-Escamez1,3,10 1GENYO-Centre for Genomics and Oncological Research–Pfizer/University of Granada/Junta de Andalucía, PTS, Granada, Spain, 2Hearing Sciences, Division of Clinical Neuroscience, School of Medicine, University of Nottingham, Nottingham, United Kingdom, 3Department of Otolaryngology, Instituto de Investigación Biosanitaria, ibs.Granada, Hospital Universitario Virgen de las Nieves, Granada, Spain, 4Department of Otolaryngology, Complexo Hospitalario de Pontevedra, Pontevedra, Spain, 5Division of Otoneurology, Department of Otorhinolaryngology, Complexo Hospitalario Universitario, Santiago de Compostela, Santiago, Spain, 6Department of Otolaryngology, Hospital Universitario de Salamanca, IBSAL Salamanca Spain, Salamanca, Spain, 7Laboratory of Experimental Audiology, Department of Physiology and Pharmacology, Karolinska Institute, Stockholm, Sweden, 8Bioinformatics Core, Luxembourg Centre for System Biomedicine, University of Luxemburg, Esch-sur-Alzette, Luxembourg, 9National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust, Ropewalk House, Nottingham, United Kingdom, 10Department of Surgery, Division of Otolaryngology, University of Granada, Granada, Spain. However, expression of uEVs miR-200a-3p and miR-29a-3p differed significantly between chronological samples (p = 0.013 and p = 0.011, respectively). Rodríguez Novoa: None. Genetic investigations included gene-panel sequencing, long-range and quantitative PCR analyses. S. Introduction: Previously, it was shown that CNVs of human satellite III (1q12) fragment (f-SatIII) and telomere repeat

(TR) reflect human cells response to oxidative stress. Head MRI showed optic nerve and chiasma hypoplasia. Funding:Hungarian Brain Research Program (Grant No. 2017-1.2.1-NKP-2017-00002). AML is characterized by wide genetic heterogeneity, complex pathogenesis and variable survival rate. They share a characteristic common phenotype including growth retardation, microcephaly, intellectual disability, cardiac defects and facial dysmorphism suggestive of Cornelia de Lange syndrome (CdLS). Mostafa: None. These findings are particularly interesting to further unravel new (modifier) genes involved in the etiology of HSCR, as well as to provide new potential markers for genetic counselling. Various known pathogenic deletions overlap with our patient's, but the majority are larger, sometimes extending into Xq22.2-Xq22.3. The most similar variant is a 1.1 Mb deletion in a female patient who had clinical features comparable to our case (Grillo et al., Eur J Med Genet 2010;53:113-6). Introduction: With the introduction of prenatal Exome Sequencing (ES), uncertainty is often a topic of debate; uncertain results may needlessly burden pregnant couples, whereas withholding results may be needlessly paternalistic. Gil-Salvador: None. The patient had also a neonatal jaundice which was related to the homozygous mutation of UGT1A1 exon 3 (c.1070A>G). The COVID-19 pandemic has accelerated the implementation of this type of teleconsultation, and has quickly made it possible to assess patient satisfaction. We will furthermore provide a financial evaluation of this novel service. P04.045.B The importance of extracutaneous organ involvement for the clinical severity and prognosis observed in incontinentia pigmenti caused by IKBKG mutationsHwa Young Kim, Jung Min Ko, Hyun Beom Song, Kyu Han Kim, Jong Hee Chae, Man Jin Kim, Moon-Woo Seong Seoul National University Hospital, Seoul, Korea, Republic of. Donors (71.4 ± 15 years) were free from neurological or psychiatric diseases. Conclusions: The prevalence of maternal UPD was 20.6% in fetal tissues. Introduction: Alzheimer disease (AD) is the most common cause of dementia, and identifying genetic factors causing changes in molecular pathways associated with AD are crucial for developing diagnostic methods and treatment therapies. P04.011.D Bone mineralization inSATB2-associated syndromeAnne Dittrich, Joyce Geelen, Jos Draaisma Rradboudumc Amalia children's hospital, Nijmegen, Netherlands. ERK phosphorylation of MET p.(Leu1130Ser) was studied after a transient transfection of 24 hours. Pre-symptomatic testing for incurable neurological conditions has previously only been offered as face-to-face appointments. This variant is not found in control databases and was not reported in literature, in silico tools predict it as deleterious, UniProt database suggest that an important protein domain is affected. Kytola: A. Kokitsu-Nakata1, Camila Wenceslau Alvarez1, Chiara Migliore2, Marina Bigeli Rafacho1, Maria Eugênia Siemann1, Rosana M. Pan Perez-Villalobos: None. Introduction: Prostate cancer (PC) is one of the most common types of cancer. While late-diagnosed PKU is unusual, the diagnosis should be considered in cases of unexplained learning challenges, psychiatric symptoms, or neurocognitive impairment, even if mild, especially if the patient was born during a period or place where neonatal PKU screening was not systematically conducted. WES analysis of five schwannomas is currently ongoing. However, many participants found this a difficult concept to grasp and often reverted to discussing individual results. Detailed pedigree analysis showed no clinical evidence of DC except premature hair graying, anemia and cancer in blood relatives across three generations. Ekinci: None. The algorithm compares the homopolymer length at each locus for each sample to an average length of microsatellite. Results: We objectified that 51 associated gèènes for myopathies were actionable with currently available data. Several strategies for PRS calculation were tested, including effects of genotype imputation and usage of sex-specific GWAS summary statistics. Regardless of patient toxicity status, the 8-Gy irradiation leads to a significant gene expression signature. As no carriers were detected in the population-based samples, only lower limit of confidence interval for OR was calculated and was found to be 14,4. BAX1, BCL2, p53, LC3, p65 (NF-kB), BRCA1, NRF2, MDM2, RAD50 and MRE11A proteins levels in the students' lymphocytes increased under stress. The portal aggregates mouse research resources for SARS-CoV-2 and other coronaviruses, including curated publications and preprints, new and repurposed mouse models, and human/mouse genes implicated in coronavirus infection pathophysiology. Beskorovainiy: None. congenital alopecia with or without neuroectodermal phenotypes including intellectual disability, epilepsy, microcephaly, genital abnormalities in males and dermatological symptoms. Phenotypes were reported by each attending physician. In total, 16 patients with t(8;21) and 6 patients with inv(16) were investigated (15 boys and 7 girls, mean age 8.5 years). Spodenkiewicz: None. Peremiquel-Trillas: None. We have completed approximately 340 exome-wide analyses over the last three years, averaging approximately 10 cases per month with a TAT of 42 days. Zieger 1, Leonie Weinhold2, Axel Schmidt1, Manuel Holtgrewe3, Stefan A. TTBK2 encodes the tau tubulin kinase 2 protein, a protein kinase involved in different cellular processes, e.g., ciliogenesis, microtubule dynamics, and tau and TDP-43 phosphorylation. Materials and Methods: We performed GWAS meta-analyses on three grip strength tests, namely with the right and left hand and the maximal score, in the ALSPAC and Raine cohorts (NALSPAC ~ 5,400, NRaine = 1,162, age range 11-13 years). P01.041.A The relevance of loss-of-function variants in the X-chromosomal gene TEX13B in azoospermia is questionable Margot J. Aortic dilatation was observed and his echocardiography showed bicuspid aortic valve. Minigenes propose splicing modification. Meiners, Yvonne J. Fasham: None. Results: Sequencing of TGFB3 revealed three mutations. Gorter: None. Using interphase FISH with centromeric DNA probes (Vysis CEP 7 (D7Z1) SpectrumGreen and Vysis CEP 16 (D16Z3) SpectrumOrange, AbbottLaboratories), we analyzed the copy number of chromosomes 7 and 16 in nine karyotypically normal ULs. Chromosome copy number was screened in 1000 cultured and 1000 non-cultured cells of each UL. All three maternal aunts did not give any hydrops fetalis births and did not carry this variant. Ziegler: None. We determined the associations between identified genotypes and analysed clinical characteristics. Radtke: None. C.M.J. Tops: None. P10.052.D Pathogenic SAMD9L variants: Differential diagnosis of CMT and potential pitfall in trio-exome analysis Katja Eggermann 1, G. PTPN11 was the most frequently mutated gene (74%). There is increasing demand for PCR-free WGS (e.g. rapid diagnosis of newborns, Tumor/Normal somatic sequencing) enabling identification of more variants without amplification-associated artifacts. Spalding: None. Négrier: None. This syndrome has been recently described by Nguyen et al. Bogomolov2, Mikhail I. Gerratana: None. The majority of PTLS cases (64%) are caused by non-allelic homologous recombination (NAHR) between repeat gene clusters on 17p11.2, resulting in a recurrent ~3.6 Mb duplication. Case report: A 36 year-old man was referred to Genetics due to facial dysmorphism, MVP and stroke at a young age. However, only 3 patients have been described in the literature to date (OMIM# 100790). In our case, we have developed a care protocol together with the different medical specialties. Gene Number(percent) of pathogenic and Likely pathogenic variants Number of mutations haven't been described earlier PTPN11 63(52%) 1 SOS1 11(9%) 2 BRAF 11(9%) NF1 9(7.4%) 3 SHOC2 8(6.6%) 1 HRAS 4(3.3%) RIT1 3(2.5%) KRAS 3(2.5%) 1 MAP2K1 3(2.5%) 2 SPRED1 2(1.65%) 1 CBL 1(0.83%) LZTR1 1(0.83%) 2 NRAS 1(0.83%) RAF1 1(0.83%) 3 Conclusions: The proportions of diseases and mutation spectrum in the group of patients with Rasopathies from the Russia were determined. P18.042.D Clinical pharmacogenetic analysis in 5,001 individuals with diagnostic whole exome sequencing data Javier Lanillos 1, Marta Carcajona2, Paolo Maietta2, Sara Alvarez2, Cristina Rodriguez-Antona1 1Hereditary Endocrine Cancer Group, Human Cancer Genetics Programme, CNIO, Madrid, Spain, 2NIMgenetics, Madrid, Spain. We hypothesize that improving the selection of patients to test based on their phenotypic presentation will increase diagnostic yield and therefore reduce unnecessary genetic testing. Joosten: None. Whitworth2, Peter D. Ilyushkina: None. The group followed a methodology based on specific formal guidelines development including 1) evaluating the likelihood of BRCAm from a combined systematic review of the literature, risk assessment models and expert quotations and 2) therapeutic values of BRCAm status for PARPi therapy in BRCA-related cancer and for management of early and advanced breast cancer. Bonduelle: None. Jongmans1,2 1Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands, 2University Medical Center Utrecht / Wilhelmina Children's Hospital, Utrecht, Netherlands, 3Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands, 4Oncode Institute, Utrecht, Netherlands. Results: The MeD-seq yielded 1541 DMRs in transcription starting sites (TSS), CpG islands and gene bodies. Introduction: Alport Syndrome (AS) is a severe inherited glomerulopathy caused by mutations in the genes encoding the α-chains of type IV collagen, the most abundant component of the glomerular basement membrane (GBM). Often, determining the underlying aetiological features of a given disease requires a multi-faceted approach. Genetics Department, Hospital Universitario La Paz, IdiPAZ, Madrid, Spain, 7Bioinformatics Section. Serey-Gaut: None. Bucerzan: None. Hierro: None. Caberg: None. The GG genotype was found to be associated with RA in the co-dominant and the dominant models (OR = 2.03, 95% CI = 1.08-3.81, p = 0.042 and OR = 1.54, 95% CI = 1.06-2.23, p = 0.023, respectively). Introduction: Complications of type 2 diabetes affect a significant proportion of patients and their prevalence, correlates with increased duration of diabetes. Kooij: None. P25.018.A Confirming rapid test diagnostics in SARS-CoV-2 infections using RT-PCR Rodica Madalina Cristea 1,2, Pompilia Petruta Apostol2, Madalina Andreea Ivan1,2, Maria Pelin1,2, Nitu Florin Robert1,2, Robert Adrian Nitu1,2, Ortansa Csutak1 1University of Bucharest, Faculty of Biology, Bucharest, Romania, 2SC Clinica Sante SRL, Bucharest, Romania. Also, there were two different mutations affecting the same codon 1181 in the NALCN gene(NM_052867.4). Magli: None. Further studies with exome analysis are ongoing. Trebušak Podkrajšek: None. Borst: None. However, a heterozygous variant of uncertain significance (VUS), in the TRIO gene c.3199_3203delinsGAGCC p.(Lys1067_Glu1068delinsGluAla) was detected. Sosero1,2, Ashwin A. Introduction: Combination of acquired and inherited risk factors can lead to disbalance of coagulation system which is related to many serious disorders. Lin: B. Disease No. cases (% of all)1 Heritability2 Best model %-improved performance (by model)3 LD pruning (r2) P-value threshold Nagelkerke R2 Allergic rhinitis 22,116 (7%) 0.20 0.9 0.05 0.012 25% (MT-dis) Asthma 45,154 (13%) 0.20 0.9 0.05 0.028 -12% (ST) CAD 25,998 (8%) 0.12 0.9 0.20 0.022 14% (MT-all) Diabetes T2 18,809 (6%) 0.28 0.1 0.999 0.036 16% (MT-quant) Hyperlipidemia 35,097 (10%) 0.15 0.9 0.999 0.21 20% (MT-all) Hypertension 112,213 (33%) 0.20 0.9 0.999 0.048 -5% (ST) Osteoarthritis 59,833 (18%) 0.17 0.5 0.999 0.014 -5% (ST) 1: Among unrelated, white-British individuals (n = 335,744). &. Notably, 3.5% of patients with variants classified as VOUS had two CNVs, each inherited from one of the two healthy parents and overlapping known and/or new candidate NDD genes, that could act by double-hit mechanisms. The application of next-generation sequencing is changing the nature of biomedical diagnosis. ETV5-deficient Sertoli cells were also found to have decreased CXCL12 levels. In the Syrian, Iraqi, and Kurdish families, the homozygous c.847G>A, in exon 13 was identified and associated with an early-onset and severe clinical presentation. The Craniosynostosis 3 (MIM 615314) phenotype, a molecular well-described form of isolated craniosynostosis, is caused by mutations in the TCF12 gene. Human face profile shows important variations between humans but no GWAS have focused on that particular phenotype so far. Conclusion: Combination of sorafenib, VPA and metformin has synergistic effects towards reduction of viability and migration potential, in contrast with angiogenic potential, where levels of VEGF-A transcript remain with no changes. Introduction: Alpha-mannosidosis is a rare inherited lysosomal storage disorder caused by mutations in the gene encoding for the lysosomal alpha-d-mannosidase, MAN2B1. Esteban-Pérez: None. Conclusion: The consortium is looking for teams interested in joining this international initiative to improve the collective expertise for the benefit of patients. Wood: None. Subnormal 30 Hz flicker ERG was found in 8 patients with SD. Conclusions: In the placenta, we confirmed the association of DNA-demethylating agent's growth restriction with oxidative/nitrosative stress. Selected variants located in different functional domains of SETD1B were functionally tested using in vitro and genome-wide methylation assays, confirming in silico predictions. Aneuploidy is the major cause of embryonic & fetal death. P02.026.C Genetic Variant Curation in GJB2 and GJB6 genes from an Argentinean cohort of hearing loss patients Paula I. Most patients develop early-onset seizures and movement disorder, such as ataxia or dysmetria associated with progressive cerebellar atrophy on brain imaging. Chiryaeva1, Alexander M. In this study, we investigated a consanguineous Pakistani family having four affected individuals with heart arrhythmia followed by ventricular septal defect in only one individual. Chałupczyńska: None. Introduction: Deficiencies of polymerase proofreading (PP) or mismatch repair (MMR) are typically acquired somatically in neoplastic cells, but can also be constitutional conditions associated with rare cancer syndromes. Short: None. Genes involved in primary COQ10 deficiency, including COQ6, should be included in gene panels for pediatric cardiomyopathy. We describe the variable spectrum of findings and clinical impacts of exome sequencing (ES) in a cohort of 500 patients with rare diseases. Stiburek: None. V.E. Montaño-Fernández: None. P23.003.C Development of biobanking in Russia: legal aspect Iurii S. By tumor proportion level (TPS), PD-L1 expression was classified as negative (TPS T) and GNS (c.811A>G, p.Arg271Gly) and classified as pathogenic and likely pathogenic, respectively, according to ACMG criteria. Through the ERN-ITHACA's expert and patient participation network, ILIAD is able to provide an infrastructure for diagnosis, highly specialised multidisciplinary healthcare, evidence-based management, and collection of secure patient data. We describe a 3-year old patient with global developmental delay recognized at an early age, characterized with hypotonia and inability to hold the head, lack of speech, inability to walk, seizures (controlled on anti-epileptic drugs) and behavioral problems. P15.021.A Improving the efficiency of EGFP editing by CRISPR-Cas9 ribonucleoprotein complexes Yana Slesarenko, Alessya Bykonya, Arina Anuchina, Milyausha Zaynitdinova, Alexander Lavrov, Svetlana Smirnikhina Research Centre for Medical Genetics, MOSCOW, Russian Federation. However, LL alleles have shown a significant positive correlation with PEDT (r = 0.46, p A; p.Gly117Ser) in one patient. After clinical, endocrinological and radiological explorations, even patients shorter than -2,5 SD remain without diagnosis. M.C.A. Cornips: None. Results: Using MDR, models of intergenic interactions of FTO rs9939609, LPL Ser447ter, and LIPC -250 G>A polymorphism with obesity were constructed. Lorenzo-Salazar1, Carlos Flores1,2,3 1Genomics Division, Instituto Tecnológico y de Energías Renovables (ITER), Santa Cruz de Tenerife, Spain, 2Research Unit, Hospital Universitario N.S. de Candelaria, Universidad de La Laguna, Santa Cruz de Tenerife, Spain, 3CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain, 4Instituto de Tecnologías Biomédicas, Universidad de La Laguna, Santa Cruz de Tenerife, Spain. Discussion: The patient's phenotype was strinkingly similar to ZTTK syndrome. The most commonly identified genes were SCN1A - 5, CACNA1A - 3, GABBR2 - 2, GRIN1 - 2, GRIN2B - 2, TSC2 - 3, SYNGAP1 - 2, SPTAN1 - 2, PCDH19 - 2, TRIO - 2, CHD2 -2, FGF12 - 2, KCNQ2 - 2, MECP2 - 2. Susceptibility to viral infection and disease progression is known to vary between geographically distinct populations. Results from multiplex ligation-dependent probe amplification analysis, glucosaminoglycans in urine, echocardiography, renal ultrasound scanning, X-ray examination of the spine and cranium were normal. Jelsig: None. Maghribi: None. N.B. Agaoglu: None. Results: We built a pilot database with around 100 recessive ASPs. We identified an average of 19.3 characteristic terms per entity. He had webbed neck. The analysis of the remaining nine families is currently ongoing, and results will be presented at the conference. Arauz-Garofalo: None. Results: Exosomal miR-146a showed an inverse association with circulating C3 and C4 complement components, proteinuria, and with histological features such as chronicity index. P08.079.A Biallelic loss-of-function mutations in WDR11 are associated with microcephaly and intellectual disabilityNatja Haag1, Ene C. - A pilot model based on hearing loss genes deletionsLena Sagi-Dain1, Idit Maya 2, Lina Basel2 1Carmel Medical Center, Haifa, Israel, 2Rabin Medical Center, Petach Tikva, Israel. Additionally, a burden test will be conducted. Subsequently, for the same samples we performed a high depth (>50×) targeted NGS of P6, the largest Y chromosome singleton palindrome. CNVs were reported in 15% of diagnosed patients and 32% of the CNVs identified were intragenic. Personality has a fundamental role in underlying a series of psychiatric symptoms. Conclusions: TSO panel is a powerful tool for detection of rare genetic disorders in clinical practice, with about 25% of diagnostic sensitivity. The aim of the study was to correlate different BCR-ABL1 FISH pattern types to survival probabilities and response in CML patients. Variant and segregation studies were confirmed by Sanger sequencing. This variation deleted the target arginine in TGFBIp without causing frameshift. Oud3, Matthias Vockel4, Sabine Kliesch2, Corinna Friedrich1, Frank Tüttelmann1 1Institute of Reproductive Genetics, University of Münster, Münster, Germany, 2Centre of Reproductive Medicine and Andrology, Department of Clinical and Surgical Andrology, University Hospital Münster, Münster, Germany, 3Department of Human Genetics, Radboud University Medical Centre, Nijmegen, Netherlands, 4Institute of Human Genetics, University of Münster, Münster, Germany. In conclusion, in one platform, optical genome mapping has the potential to identify a broad range of genomic abnormalities, and to improve the characterization of SVs. A. P09.113.B MINPP1 prevents intracellular accumulation of inositol hexakisphosphate and is mutated in Pontocerebellar HypoplasiaEkin Ucuncu1, Karthyayani Rajamani1, Miranda S. Chrzanowska: None. Further "enablers" that would facilitate implementation into practice included recognition of the potential to reduce adverse drug reactions, improve patient motivation and, from the patients' perspective, alignment with a general interest in genetic testing. Lucassen2, Angus J. P20.037.D Weighted gene co-expression network analysis identifies critical altered pathways and hub genes in high-grade serous ovarian cancer Magdalena Niemira 1, Karolina Chwialkowska2, Agnieszka Bielska1, Anna Szalkowska1, Iwona Sidorkiewicz1, Urszula Korotko2, Anna Erol1, Justyna Raczkowska1, Gabriela Sokolowska1, Katarzyna Doroszko1, Sylwia Chludzinska3, Jacek Szamatowicz4, Pawel Knapp5, Miroslaw Kwasniewski2, Joanna Reszec3, Marcin Moniuszko6, Adam Kretowski1,7 1Clinical Research Centre, Medical University of Bialystok, Bialystok, Poland, 2Centre for Bioinformatics and Data Analysis, Medical University of Bialystok, Bialystok, Poland, 3Department of Medical Pathomorphology, Medical University of Bialystok, Bialystok, Poland, 4Department of Gynecology and Gynecological Oncology, Medical University of Bialystok, Bialystok, Poland, 5University Oncology Center, Medical University of Bialystok, Bialystok, Poland, 6Department of Regenerative Medicine and Immune Regulation, Medical University of Bialystok, Bialystok, Poland, 7Department of Endocrinology, Diabetology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland. Brno conference to be held at the Augustinian Abbey: "Bicentennial of the birth of Gregor Johann Mendel", July 20-23, 2022 (www.mendel22.cz) M. Tele-counseling was offered when suitable. Conclusions: Our previous work reported a high-confidence microRNA-mRNA interactions allowed us to identify microRNA-binding sites, mutations in which could potentially play role in the development of human cancer and hereditary disorders. Conclusions: Our data showed that MYH7 p.(Arg1712Gln) is a pathogenic founder variant in HCM and that cardiac screening should be pursued after the seventh decade in healthy carriers, especially women. P17.004.C Gene-SCOUT: gene-based biomarker signatures can assist identification of novel genes from phenome-wide association analyses Lawrence Middleton, Quanli Wang, Andrew Harper, Abhishek Nag, Dimitrios Vitsios, Slavé Petrovski AstraZeneca, Melbourn, Royston, United Kingdom. Al-Saegh: None. Financial support: French Government Scholarship. A total of 34 distinct variants (including 4 novel) and 64 different genotypes were determined. An international group of experts including geneticists, medical and surgical oncologists, pathologists, ethicists and patient representatives was commissioned by the French Society of Predictive and Personalized Medicine. However, this association could not be replicated in the PsyCourse sample. HCM causing TPM1 mutations act in a dominant-negative, poison polypeptide mechanism, altering this delicate balance and increasing the myofilament's calcium sensitivity causing hypercontraction and hypertrophy. CS typically causes coarse facial features, macrocephaly, growth and developmental difficulties and skeletal, ocular and neurological problems. Second, we studied whether genetic risk scores for insulin resistance, comprising 13 loci associated with FI or 53 loci associated with a combination of high FI, high triglycerides and low HDL cholesterol (FI-TG-HDL), contribute to fetal or maternal genetic effects on birth weight. Talantova1, Olga G. Stojiljkovic: None. Speakers Bureau/Honoraria (speakers bureau, symposia, and expert witness); Modest; Sanofi Genzyme, Shire (now part of Takeda), and Greenovation Biotech GmbH. Consequently, FXTAS is often misdiagnosed as spinocerebellar ataxia (SCA) or Parkinson's disease (PD). All known variants were called correctly and could be phased correctly as well. Ponce: None. Tomczuk: None. E.C. Wirrell: F. Cherino: None. Materials and methods: We present a case of a four month old girl, who was referred to the genetic department because of macrocrania (50cm, Z score = +7.44 SDS, >p98), frontal bossing, generalised hypotonia, delay in motor acquisitions. Sigaudy: None. The study was supported by Russian Science Foundation (№20-15-00227). Mota-Freitas: None. marzioglu ozdemir: None. Bacillus Calmette-Guerín (BCG) being TB vaccine also provides non-specific protective effects against other infections through "trained innate immunity". Martin-DeSaro: None. Pregnancy and perinatal course were uneventful. Material and methods: 118 Georgian individuals suspected for FMF were screened for MEFV gene mutation variants M694V, V726A, M680I(G/C), M680I(G/A), F479L, E148Q, M694I, R761H, P369S, 1692del, K695R, A744S using PCR methods. Glavac: None. Methods: The patient was evaluated by a multidisciplinary team. Jabot-Hanin: None. ALK inhibitors like crizotinib have shown tremendous antitumor activity for ALK-positive cancer. However, the increased effort needed to familiarise analysts with novel genes and variants increases turnaround times and may lead to delays in reporting. Mori: None. Conclusion: Hypermethylation of the ESR1 gene promoter region in women was associated with placental insufficiency and perinatal loss. Ezquerra-Inchausti: None. Holtgrewe: None. Neurological examination evidenced milder symptoms and the presence of pes cavus, scoliosis and distal weakness. Assuming all experimental steps are performed according to a high standard, the very high success rate of TUDP could be the effect of the rigorous patient selection criteria used. Minuti: None. Results: We identified 16 likely disease-causing novel variants in the following HSAN/CIP genes: ATL3, DST, FLVCR1, NGF, NTRK1, PRDM12, SCN9A, SPTLC2 and WNK1. Kaname: None. Kempe 1,2,3, Öznur Yilmaz2, Tobias T. (ii) ITHACA-specific cohorts We are collecting genetically unsolved patients for the following syndromes: Moebius/Poland, Goldenhar, Wildervanck, Baraitser-Winter, primary microcephalic dwarfism, MURCS, RAS-opathies and 'Rett-like'-phenotypes. Employment (full or part-time); Significant; Bioscientia Healthcare GmbH. Here we report twelve novel patients carrying either de novo (4/12) or inherited (8/12) heterozygous pathogenic variants in C1R and C1S, in order to characterize their clinical phenotype, with a focus on the vascular features. Gregersen1,6 1Department of Clinical Genetics, Aarhus University Hospital, Aarhus N, Denmark, 2Department of Public Health, Aarhus University, Aarhus, Denmark, 3Department of Pediatrics, Herning Hospital, Herning, Denmark, 4Department of Cardiology, Aarhus University Hospital, Aarhus N, Denmark, 5Department of Pediatrics and adolescence, Aarhus University Hospital, Aarhus N, Denmark, 6Centre for Rare Diseases, Department of Pediatrics and Adolescence, Aarhus University Hospital, Aarhus, Denmark. Both variants contributed to a complex phenotype for 10 patients. Baldan: None. Salman: None. Deep intronic variants can alter splicing, including intronic regions in mRNA by activating/creating splicing sites or splicing regulatory elements (SREs). Materials and Methods: Whole exome sequencing was performed using Illumina HiSeq 4000 instrument on four different patients who presented with epilepsy and dysmorphic symptoms. Introduction: Microdeletions of various sizes in the 2p16.1-p15 chromosomal region have been assembled together under the 2p16.1-p15 microdeletion syndrome. NGS performance on all specimens was high, with 2.5% overall failure rate and reliable detection of EGFR variants at variant allele frequency as low as 2%. Bonati3, Paola Bettinaglio1, Cristina Battaglia1,2, Roberta Bordoni2, Paola Riva1 1Department of Medical Biotechnology and Translational Medicine, Università degli Studi di Milano, Milano, Italy, 2Institute of Biomedical Technologies, Consiglio Nazionale delle Ricerche, Segrate (Milano), Italy, 3Medical Genetics Unit, IRCCS Istituto Auxologico Italiano, Milano, Italy. 259/603 (43%) patients had moderate to profound intellectual disability and/or global developmental delay. Results: 21 patients were homozygous and one compound heterozygous for c.694T>G/p.(Phe232Val) in EIF3F. Vandevelde1 1Department of Quality of Laboratories, Sciensano, Brussels, Belgium, 2Center of Human Genetics, CHU of Liege, University of Liege, Liège, Belgium, 3Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium, 4Center of Human Genetics, Institut de Pathologie et de Génétique, Gosselies, Belgium, 5Center for Medical Genetics, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Brussels, Belgium, 6Center of Medical Genetics, Antwerp University Hospital and University of Antwerp, Edegem, Belgium, 7Center for Human Genetics, University Hospitals Leuven, Leuven, Belgium, 8Center of Human Genetics, Hôpital Erasme, Université Libre de Bruxelles, Anderlecht, Belgium, 9Center for Human Genetics, Cliniques universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium. Lanting: None. P20.035.B From man to mouse: The discovery and validation of CYR61 as a regulator of body composition Sophia Metz, Katja Thorøe Michler, Matthew Paul Gillum, Tuomas Oskari Kilpeläinen Novo Nordisk Foundation Center for Basic Metabolic Research, Copenhagen, Denmark. Our investigation was from the viewpoint of hypothetical implementation of PGS analysis as a novel biomarker test within the UK National Health Service. E.Y. Zakharova: None. Serra: A. The level of urinary glutamic acid was also normal. Ahmed3, Kristyn L. Segur - Bailach: None. Vlachopoulos: None. Muaremoska-Kanzoska: None. Testing the 48 markers in plasma cfDNA by MSREqPCR (44 CRC, 44 controls) provided in ROC analysis an AUC>0.85 for WT1, PENK, SPARC, GDNF, TMEFF2, and DCC. Another explanation for the success rate of TUDP refers to the higher parental age in Italy, which is associated with the easier identification of de novo dominant exonic mutations, present in 68% of cases solved by TUDP. Data analysis was performed using BlueFuse Multi 4.5 software. Ramakumaran24, Alistair T. Besides, his mother had toe amputations compatible with amniotic bands, dentine defects, syringomyelia and Arnold-Chiari malformation. Mean age: 6 years old (1.5-15). Serrano: None. Results: On physical examination, his height was 149,4 cm (-3,92 SDS), weight was 38,2 kg (-4,43 SD). Doherty: None. The best performing tools for the ABCA4 DI variants were SpliceAI, SpliceRover, MaxEntScan, NNSplice and Alamut 3/4. Steffens3, David Melzer1,3 1University of Exeter, Exeter, United Kingdom, 2University of Newcastle, New South Wales, Australia, 3University of Connecticut, Farmington, CT, USA. SLCO1B1 rs4149056 is a potential marker of lopinavir response, especially in Italian population. He had several dysmorphic features-macrocephaly, protruded forehead, prominent eyes, receding mandible, large ears. P11.063.A Role of imprinting disorders in short children born SGA and Silver-Russell syndrome spectrum Masayo Kagami 1, Tomoko Fuke1, Akie Nakamura1,2, Takanobu Inoue1, Sayaka Kawashima1, Kaori Isno-Hara1, Shinichiro Sano1,3, Kazuki Yamazawa1,4, Maki Fukami1, Tsutomu Ogata1,3 1National Research Institute for Child Health and Development, Tokyo, Japan, 2Hokkaido University Graduate School of Medicine, Sapporo, Japan, 3Hamamatsu University School of Medicine, Hamamatsu, Japan, 4National Hospital Organization Tokyo Medical Center, Tokyo, Japan. Allelic score of each FMR1 allele was determined using our mathematical model, as was XCI pattern using HUMARA. Kyurkchiyan: None. Aim: The goal of the EPIGENOME project is to identify differentially methylated regions (DMRs) for selected habits factors including diet, physical activity and stressful experiences. The results are being compared and meta-analyzed with those in the MESA cohort and the Sanford Health System. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Significant; Japan Agency for Medical Research and Development. Condon: None. Poloznikov: None. Smirnova2, Olga E. Results: Seventy-three patients with syndromic RD were included, being 22q11 deletion, Noonan and Prader-Willi syndromes the most frequent. Spurdle: None. Simões: None. Arilla-Codoñer: None. Hence, due to the gene dosage effect, X-overexpression may cause an increased gene dosage and that may cause susceptibility to autoimmune disease. Diagnosing EDS is challenging due to the high clinical variability and the lack of a diagnostic biomarker in paediatrics. Bladergroen: None. Noorozi: None. Less than 10 patients are reported in literature to date, we thus collect patients for collaborative clinical research on HNRNPR variants in order to understand the phenotypic spectrum of this disease. In addition, using 3D culture we provided a comprehensive understanding regarding exosome internalization in 3D structures. Further, optimal loading of Rad51 onto RPA coated ssDNA requires MDC1. Conclusions: Reporting of secondary findings is important both for determining the tactics of further treatment, and for family consulting. Moreover, interactive HTML reports can be generated to filter and select variants of interest. Immesoete2, B. D. Left ureterostomy and right ureter endoscopic dilation were performed at 2 months. Introduction: Every year, approximately 1-6/1000 children are born with severe to profound hearing loss (HL) and for this group of patients cochlear implantation (CI) is the treatment of choice. Casalone: None. Zare Ashrafi: None. However, there exist many other genes involve in this process.We describe the case of a 54-years-old woman with an incidental finding of absence of uterus, ovaries, prostate or seminal vesicles, after a TC scan performed for other pathologies. Materials and Methods: To further extend these data, a total of 206 MPM patients (93 from a previous study, 113 new) were screened by targeted-NGS for germline PVs in cancer-predisposing genes. No losses were observed in the patient blood lymphocytes. I.R. Imatdinov: None. Cario: None. 5,5 % patients had combined variants in pathogenic BRCA1 with variants of P53 gene (5382insC/G119C - 4,8%; 4153delA/G119C - 0,6%). Clinical-radiological examination showed rhizomelic shortness of stature, femoral bowing, abnormality of metaphyses, delayed ossification of carpal bones and patella. Petrini: None. Bakkeren1, Katinka Dijkstra2, Sam Riedijk1 1Department of Clinical Genetics, Erasmus Medical Centre, Rotterdam, Netherlands, 2Department of Psychology, Education & Child Studies, Erasmus University Rotterdam, Rotterdam, Netherlands, 3Center for Fetal Diagnostics, Aarhus University Hospital, Aarhus, Denmark, 4Department of Clinical Medicine, Aarhus University, Aarhus, Denmark, 5Department of Clinical Genetics, Aarhus University Hospital, Aarhus, Denmark. Class I and II HLA alleles were inferred from whole-genome genotyping data using SNP2HLA and Beagle_v3.3 tools. No. PV in MUTYH (LRG_220t1) Colorectal polyps (age) Colorectal cancer (age) Personal history of other tumours (age) Family history of cancer (age) Family history of polyposis 1. J.E. Kolomenski: None. The bioinformatic analysis suggested a pathogenic effect likely related to the absence of the described mutation in healthy people. Better characterization of risk genes could enable the stratification of patients according to the main molecular mechanisms of pathogenesis, supporting development of tailored and personalised treatment of AD. Alés Martínez36, Pascal Pujol1 1CHU Montpellier, MONTPELLIER, France, 2European Institute of Oncology, MILAN, Italy, 3University of Glasgow, GLASGOW, United Kingdom, 4Chaim Sheba Medical Center, TEL-HASHOMER, Israel, 5Institut Català d'Oncologia (ICO), HOSPITALET DE LLOBREGAT, Spain, 6Federico II School of Medicine, NAPLES, Italy, 7Oncohealth Institute, MADRID, Spain, 8Centre Léon Bérard, LYON, France, 9Centre Jean Perrin, CLERMONT-FERRAND, France, 10The Research Institute of the McGill University, MONTREAL, QC, Canada, 11The Institute of Cancer Research, LONDON, United Kingdom, 12Women's College Research Institute, TORONTO, ON, Canada, 13University of Texas MD Anderson Cancer Center, HOUSTON, TX, USA, 14Clinique de Genolier, GENOLIER, Switzerland, 15The Institute of Genetics and Molecular and Cellular Biology, STRASBOURG, France, 16Istituto Nazionale Tumori "Fondazione G. Urbanová: None. The adoption of gene panels, clinical exome and whole exome sequencing (WES) increased the diagnostic yield even for complex syndromic patients, often leading to an expansion of the phenotypic spectrum of a given gene. Chaumette: None. R.H. Galjaard: None. Moghaddasi: None. Bioinformatic analysis was used to mine for 94 MS related risk variants with ≥ 2 reports confirming MS risk association. P08.056.B A case report of O-Donnell-Luria-Rodan syndrome with a novel truncating variantPilar Carrasco Salas1, Rosario Mateos Checa2, Ana Serrano Mira1, Marina Oliva de Agar 3 1Genetic Unit, Clinical Analysis Department, Hospital Juan Ramón Jiménez, Huelva, Spain, 2Neuropediatric Unit, Pediatric Department, Hospital Juan Ramón Jiménez, Huelva, Spain, 3Genetics, Reference Laboratory, Barcelona, Spain. Here we provide, for the first time, an exome-wide analysis of their genetic variation. F.P. Crawley: None. Boven15, Jan D. Peutz-Jeghers syndrome (PJS) (MIM 175200) is an autosomal dominant disease caused by pathogenic variants in the STK11 gene (alias LKB1). The clinical data for these 5 probands and their 7 relatives showed that all the probands displayed a classical form of MFS, with the involvement of skeletal, cardiovascular, and/or ophthalmological systems. The diagnosis in the first sister was achieved by a NGS microcephaly genes panel. Drug-induced ECG monitoring and genetic testing provide powerful early-warning systems. Hajek: None. 8/40 BRCA1/2-wildtype samples had scores above the thresholds and 32 below. CAPOS syndrome combines progressive hearing loss (auditory neuropathy type, (AN)), optic atrophy, hypotonia, and cerebellar ataxia. Tsepilov2,3, Yurii S. Olla: None. Belemezova: None. Crossing machine-learning and network analyses, we identified 25 microRNAs. Their 438 gene targets were enriched in schizophrenia GWAS genes and synaptic processes. Employment (full or part-time); Modest; GeneDx. S.A. Schrier Vergano: None. Korendowych: None. Quattrone: None. Kavousi: None. We demonstrated enzymatic activity defects for PIGG variants in vitro in a PIGG/PIGO double knockout system. Hospital UyP La Fe, Valencia, Spain, 7Prenatal Diagnosis. Mironska: None. Median age at testing was 38 months while the median age at first seizure was 27 months. Conclusion: Our results highlight a high rate of P/LP variants in CPGs in young Brazilian patients with sarcomas (19.8%) and we expect to collaborate with the definition of effective and adequate screening strategies for these patients. Acknowledgements: We thank brain donors and relatives for generous donation and the Neurological Tissue Bank of the Biobanc-Hospital Clinic-IDIBAPS. The sequencing was performed with high coverage (250 x) and the obtained variants were filtered by stringent criteria. P17.019.B MGvizCNA: a precision medicine webapp with CNA evidence scoringPedro Pons-Sunyer1, Jose M. The work was carried out within the framework of the state assignment of the Ministry of Science and Higher Education of the Russian Federation (project FSRG-2020-0№14). Zahra: None. Methods: We investigate the clinical utility of genotyping arrays by: 1) technical validation of common and rare variants 2) offering polygenic risk scores (PRS) as primary utility in clinical practice, 3) prospectively counseling and eligibility of feeding back secondary findings (pharmacogenomics, ACMG mutations) using arrays. Conclusions: RPL3L is a novel disease causing gene in DCM accounting for at least 8% of neonatal cases. Morris: None. Determining the molecular etiology allows for personalised patient management and surveillance, and recurrence risk estimation for families. At age one, she started with treatment refractory epilepsy. P12.094.B Characterization of recurrent breakpoints in head and neck cancer Nerea Gestoso-Uzal 1,2,3, Juan Luis García2,3, Javier Fernández-Mateos1,2, Luis Angel Corchete2,3, Sonia Carretero-Domínguez1,2,3, Paula García-Vallés1,2,3, Abel Martel-Martel1,2, Edel Del Barco2,4, Ana Belen Herrero1,2,3, Rogelio González-Sarmiento1,2,3, Juan Jesús Cruz-Hernández1,2,4 1Molecular Medicine Unit, Department of Medicine, University of Salamanca, Salamanca, Spain, 2Biomedical Research Institute of Salamanca (IBSAL), University Hospital of Salamanca-USAL-CSIC, Salamanca, Spain, 3Institute of Molecular and Cellular Biology of Cancer (IBMCC), University of Salamanca-CSIC, Salamanca, Spain, 4Medical Oncology Service, University Hospital of Salamanca-IBSAL, Salamanca, Spain. DNA was isolated from blood. Say: None. We also suggest to orient practices toward a systemic approach using a multidisciplinary team or network to provide resources for dealing with uncertainties in interpreting results or situations that require additional technical or clinical skills and, if necessary, to allow for joint consultations with both a geneticist and a non-geneticist medical specialist. Sancho: None. Nazzaro: None. Hoogerbrugge8, R. Conclusions: Our data suggest that variations in POLG gene might be important in cervical cancer carcinogenesis. P18.022.D Gene set enrichment analysis of basal and in vitro irradiation gene expression differentiates breast cancer patients with late skin radiotherapy toxicity Ester Aguado-Flor 1, María J. Volkov2, Oxana M. P19.002.B Community-based countrywide analysis of variants of the lactase-phlorizin hydrolase gene and their pathological correlates in LibyaAriej Mohammed1, Inas M. Geurts-Giele, Robert M. Our study suggests that different splicing types may have different enrichment patterns of causal effects on different cancers. Results: Our method successfully predicted the end-point protein level in 8 pathways. For 2018, postal codes were used to compare NIPT uptake between socioeconomically disadvantaged neighborhoods and other neighborhoods. In 4 patients with genotype [p.L541P, p.A1038V] «severe» phenotype of Stargardt disease was found: with large defect of the ellipsoid zone, severely subnormal macular ERG (MERG) to red stimulus and subnormal 30 Hz flicker and full-field maximal ERG. (iii) Ultra-rare patients All ~80 Health Care Providers in ITHACA are collecting (ultra-)rare unsolved patients. Psychomotor developmental delay was observed since infancy, and then she was diagnosed with mixed developmental disorder, learning difficulties. This new long read sequencing strategy is an attractive alternative to current short read sequence technologies with limited phasing capacity. Skoblov: None. P04.028.A Peds2Gene study: clinical and molecular delineation of a Spanish cohort of pediatric patients with Ehlers-Danlos Syndrome Laura Plaza, Antonio Federico Martinez-Monseny, Dídac Casas, Asunción Vicente, Francesc Palau Hospital Sant Joan de Deu, Barcelona, Spain. MiR-23b-5p directly targets PLK2-rs15009 G allele. Results: In total, 887 women were included in this analysis. P20.039.B Transcriptome analysis of the effects of melanocortin and tuftsin analogues in rat brain Ivan B. Methods: Pediatric patients diagnosed with RD associated with high physical and psychological comorbidities attended at a tertiary hospital were recruited (August to October 2020). Kuil: None. PM being a frequent tool in cancer care, it seems important for patients to understand what PM really implies in order to promote a better understanding and avoid oversized hopes.This research was funded by French National Cancer Institute, grant number 2018-164 V. De Maria: None. Barcos: None. The conservative PPV for vanished twin gestations was 460/786 (58.5%). Prabhu: None. SNP arrays (750K) of family members yielded possible disease-associated loci on chromosomes 6 and 10. Conclusions: These first findings encourage the implementation of transcriptomics in the workup of PID patients to improve diagnosis and patient management. Kalim: None. Methods: Cytogenetic analysis was performed on 20 metaphases, stained with GTG bands, from three independent cultures. Results: All patients manifested decreased vision, photophobia and elevated thresholds of dark adaptation. Introduction: The triggering factors for the disease pathways leading to idiopathic dilated cardiomyopathy (DCM) are still elusive. The research of small intragenic YY1AP1 deletions in our local database identified the same homozygous variant in another individual presenting with cutaneous syndactyly, cardiac malformation and intellectual disability and referred for an unspecific malformative syndrome. Codeine and clopidogrel require more attention in giving prescription for 25% and 8% of newborns having a decreased function of CYP2D6 and CYP2C19 enzymes respectively. A recurrent COL4A5 variant p.Gly624Asp in 15 patients (nine males and six females) was identified. Leuzzi: None. Montaño1, María Victoria Gomez del Pozo1, Natividad Gallego Onís1, María Esther Rubio Martín1, Pablo Lapunzina1,2,3, María Palomares-Bralo1,2,3, Sixto García-Miñaúr1,2,3 1Instituto de Genética Médica y Molecular (INGEMM) Hospital Universitario La Paz, Madrid, Spain, 2CIBERER, Centro de Investigación Biomédica en Red de Enfermedades Raras, ISCIII, Madrid, Spain, 3European Reference Network, ERN ITHACA, Madrid, Spain, 4Servicio de Oncología Médica, Hospital Universitario La Paz, Madrid, Spain. In addition, we identified CNVs of uncertain clinical significance in 18/239 (7.5%) of cases. Tabarki3, M. Both these identified mutations are novel and classified as likely pathogenic as per ACMG guidelines. Materials and Methods: Consecutive cases referred with chronic and progressive ataxia from the last 15 years. We performed chromosomal microarray followed by duo exome sequencing for the living proband and sixth abortuses. Signal peptide-CUB-EGF domain-containing protein 3 (SCUBE3) is a member of a small family of multifunctional secreted or cell surface-anchored glycoproteins functioning as co-receptors for a variety of growth factors. Moreover, all the peptides tested had a strong effect on the expression of genes (e.g., RT1-Ba, Cxcl13, RT1-Db1, RT1-Da) associated with the immune system. Ownership Interest (stock, stock options, patent or other intellectual property); Significant; Genos Glycoscience. Descriptive statistics and a thematic analysis were used to analyze data. Závacká: None. Materials and methods: For a set of genes, the analysis of genomic databases and refereed foreign scientific articles on the following keywords was performed: "colorectal cancer", "mutation", "miRNA", "CNV", "single-nucleotide polymorphism". Danesh: F. Rawlins1,2, Barry A. Abzianidze: None. The analysis also documented a copy number gain of Chromosome 11, pointing out a structural genomic rearrangement resulting in the duplication of the mutated HRAS allele as a second hit in the tumor. Amongst them, ARFGEF1/BIG1, involved in axon elongation, neurite development and polarization processes, has been previously suggested as a candidate gene for rolandic epilepsy, familial febrile convulsions and epileptic encephalopathy. Curetean: None. Alvarez-Estape: None. Tan2, Matthias Begemann1, Lars Buschmann1, Petra Hoschbach3, Angeline H. Dysplasia of the nails, absent/hypoplastic patellae, presence of iliac horns and elbow deformities are the cardinal features. Desaphy: None. This pandemic led the genetic counseling in Israel to suddenly change format to remote methods (either telephone or video-based counseling). Here we suggest the presence of a common ancestor in whom this variant arose and date its origin about 200 years ago. Moreover, this case emphasizes the complexity of molecular diagnosis in genetic tumor risk syndrome suspected patients, as in many of these genetically unresolved patients an obvious genotype-phenotype correlation often cannot be found. The project is built on existing data of 924 European children from the The Human Early-Life Exposome (HELIX) Project. In the HLA association studies, HLA-A*11:01:01:01 [Pc = 0.013, OR = 2.26 (1.27-3.91)] and HLA-C*12:02:02:01-HLA-B*52:01:01:02 [Pc = 0.020, OR = 2.25 (1.24-3.92)] were found to be significantly associated with the severity of COVID-19. P15.010.B Optimized shallow whole-genome sequencing for large CNV detection in rare genetic disorders Anett Marais, Krishna Kumar Kandaswamy, Antonio Romito, Natalia Ordonez, Dan Diego Alvarez, Katja Bruesehafer, Volkmar Weckesser, Peter Bauer, Jonas Marcello Centogene AG, Rostock, Germany. All patients share a similar phenotype to our patient, with developmental delay, hypotonia, feeding problems, behavioral disorder, microcephaly, strabismus, digits abnormalities and facial dysmorphism. These results will provide new evidence that could give opportunities to improve treatment of osteosarcoma patients. Conclusions: The identification of biallelic mutations in 4 different ASD families provides further support for a role of CACNA1H in ASD susceptibility, and for the first time highlights it as a candidate gene in ASD, acting in a recessive mode of inheritance.Supported by the Italian Ministry of Health (Grant GR-2013-02357561). Conclusions: The variants of the TNF-α and CCR5 genes was the genetic predictor of increased need for respiratory support in patients with COVID-19 pneumonia. His microarray analysis revealed that 3,3Mb sized heterozygous deletion on 6p25 including FOXC1 gene. No significant difference in either quality or viability between control and mitochondrial embryos was found. Atalar Aksit: None. Objectives: The aim of this study was to assess non-small cell lung cancer (NSCLC) female patients' hotspot mutations in oncogenes in formalin-fixed, paraffin-embedded (FFPE) tumor DNA and plasma cfDNA samples. Ophthalmologic investigation revealed bilateral diffuse corneal clouding and otherwise normal results. Using an integrative framework, we annotated the 330 variants included in this PRS to the genes they associate with, and performed gene-set enrichment analysis. Skrzypczak-Zielińska: None. Methods: A cohort of 120 probands, with a median age of 5 y.o, primarily studied by targeted or clinical exome, and most of them without a clear clinical diagnosis (mainly, neurodevelopmental disorders) was extended to trio analysis. Andrew: None. Whole exome sequencing identified a single candidate variant genome wide, located in the autozygous region, in the MNS1 gene (NM_018365.2:c.407_410del;p.(Glu136Glyfs*16)). In a patient 1, 6 y.o. o boy with ataxia, hypoglycemia, episodes of lactic acidosis WGS showed heterozygous missense variant c.1372A>G; p.(Asn458Asp) in the PC gene and the loss of heterozygosity on PC cDNA. Materials and Methods: We describe 7 unrelated probands with clinical features highly suggestive of Noonan syndrome. Haplotypes were generated to determine the better contribution of VEGF polymorphisms to breast cancer risk. Maximal ERG was reduced in 6 patients with SD. Hol 1, Roland P. A.S. Glotov: None. Implicated genes revealed enrichment in ASD-associated biological processes and pathways. The c. Twelve samples with known genetic aetiology were used to evaluate the performance of the NGS amplicon-based test. de Vlaming: None. X-ray showed no vertebral abnormalities. This, alongside review of published cases and UK Biobank findings, clearly refutes an association of SCN9A with epilepsy. P18.030.D Pharmacogenetics of chemotherapy response in osteosarcoma: a genetic variant in SLC7A8 is associated with progressive disease Evelien G. Preliminary Sanger results have confirmed that the NGS panel is identifying true variants, but substantial drop off of putative variants was observed after segregation analysis. One interpretation is used by clinicians and counsellors (essentially 'the likelihood that the variant will cause a phenotype'). Křepelová: None. The workflow is implemented in Snakemake and Python, with all software dependencies managed via conda. Results: The LEF1 mRNA expression of B-cell ALL patients was higher than the controls (LEF1-totalp = 0.011, LEF1-long p = 0.026). Regarding (1), male gender, ageing, and low educational level were associated with MS higher values (p-value 5,000x) Illumina sequencing of 195 common autosomal single nucleotide polymorphisms (SNPs) and 13 sex chromosome loci. Introduction: Sudden death (SD) due to ventricular fibrillation (VF) during acute myocardial infarction (AMI) is one of the leading causes of death worldwide. Materials and Methods: Conventional cytogenetic and FISH analyses of both abort tissues were carried out according to standard procedure, following tissue culture. The mother had also unilateral coronal craniosynostosis, unilateral proptosis and unilateral ptosis, longitudinal splitting of nails and clinodactyly. Pro224Leu variant had ~100% binding. Five of them, CDK19, NCALD, ARHGEF12, HECTD4 and PTPN11 were located in four new loci. Quality was assessed using the QUADAS-2 tool. Results: Six patients were withheld from the donation process given their family or personal history that required further investigation. Conclusions: It is difficult to predict genotype/phenotype relationship in patients affected by alpha- mannosidose. Results: We have identified 5 missense, 1 nonsense, 1 frameshift mutation and 1 in-frame deletion. So far, more than one hundred high-confidence susceptibility genes have been identified and recent efforts have led to an ever-growing list of ASD candidate genes. Here we use Prader-Willi syndrome as an example of how one method i.e. long-read whole genome nanopore sequencing, can provide detailed insights into the underlying genetic and epigenetic causes of a rare inherited genomic disorder. We found that Crisp1-/- and Crisp4-/- sperm had altered periodicity of flagellar oscillations between cycles and lowered flagellar amplitude, reduced oscillating frequency of the flagella and reduced rates of energy dissipation along the flagella. The RNA samples were extracted using RNA/DNA/Protein PurificationPlus MicroKit (NorgenBiotek). Gézsi: None. We investigated variance of alcohol consumption explained by genetic factors in various population subgroups including sex, age, and in relation to central tendency. Introduction: Hereditary amyloid transthyretin amyloidosis with polyneuropathy, besides its chronicity and devastating progression, poses a strong psychological impact on patients and their relatives. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Modest; German National Academic Foundation, Carl Duisberg Program by the Bayer Foundation. Filippenkov 1, Vasily V. Costa3, Ana C. The French bioethics law still firmly forbids the clinical application, however the use of genome editing in human embryos for research purposes is debatable in the French Parliament. Lupski1,4 1Baylor College of Medicine, Houston, TX, USA, 2Kuwait University, Safat, Kuwait, 3The University of Texas Health Science Center at Houston, Houston, TX, USA, 4Texas Children's Hospital, Houston, TX, USA, 5Pacific Northwest Research Institute, Seattle, WA, USA. Benedetti: None. (iv) Unsolvable syndromes We aim to unravel the genetic etiology of Aicardi, Gomez-Lopez-Hernandez, Pai, OAFNS and Hallermann-Streiff syndrome. It also confirms that vascular complications are possible, although they are not frequent, which leads us to propose to carry out a first complete vascular evaluation after the diagnosis. Journel: None. Aris-Meijer1, Els L. Šamarina: None. A.F. Martinez-Monseny: None. Plevová: None. P15.036.D Gene editing strategy for alpha-1 antitrypsin deficiency through CRISPR-cas9 in liver organoids Sara Perez-Luz 1, Gema Gomez-Mariano1, Ignacio Perez de Castro1, Iago Justo2, Alberto Marcacuzco2, Loreto Hierro3, Cristina Garfia3, Beatriz Martínez-Delgado1 1IIER, Madrid, Spain, 2Hospital 12 Octubre, Madrid, Spain, 3Hospital La Paz, Madrid, Spain. Michailova1, Andrey V. Receiver operator curves, accuracy, sensitivity, specificity, positive predictive value, negative predictive value and Mathew's correlation coefficient were used to evaluate the performance of each tool on the different datasets. This is a heterozygous missense substitution that leads to Gly12Ala mutation in a protein sequence that corresponds to transactivation domain 1. Touati: None. Next, we performed a functional enrichment analysis, based on Gene Ontology: Biological Process. J.J. Mulvihill: None. Cussenot: B. Reghunathan: None. The expanding of frontonasal process can be contributed with the fusion of upper lip and palate failure. Materials and Methods: We evaluated our FISH results of CD138 (+) plasma cells separated from bone marrow aspirates. Couch: None. P23.036.D Patient perspectives on making decisions in predictive genetic testing and in responses to fetal cardiac anomalyShane Doheny1, Lisa Ballard2, Anneke M. Moreover, advanced inherited retinal dysfunction represented by waxy pallor optic disc, attenuated vessels, RPE mottling with intraretinal bony spicules pigmentations and central foveal atrophic changes in both eyes with bilateral sensory neural hearing loss and amelogenesis imperfecta. Muñoz-Barrera: None. Results: Genome-wide significance threshold (5.10-8) was reached in the discovery sample on chromosome 9 for the pNFs phenotype. Interestingly, PADI2 expression was compensationally induced in CD11b+ cells of PADI4-/- mice. A.A. Vorontsova: None. Nearly all (>99%) demultiplexed reads were on target to CYP2D6. The allele and genotypic frequency of each variant were used to establish its distribution among the three locations. Boudko5, Brecht Guillemyn1, Tim Van Damme1, Sanne D'hondt1, Sofie Symoens1, Sheela Nampoothiri6, Douglas B. In 4 of these 5 patients, metastases were confirmed. Gimalova: None. MACROD2 is a gene involved in DNA repair, cell signaling, gene transcription, and chromatin remodeling. RTL data were analysed by gender and reproductive history. Appraisal of discrepancies by experts is typified by shock at developments and possibilities, and an inability to establish a common language between disciplines and research groups. Eng: None. Krivokapic: None. Inclusion lasted from 2013 (UMCU) and 2017 (UMCG) up until April 2020. Results: We revealed that MAD2L2 knockdown increases HDR approximately 5 times (10.9% vs 2.1% control HDR level, p = 0.027). Amniocentesis was performed to exclude placental mosaicism, followed by Vista™ Chromosome Sequencing technology - 12qterminal duplication was confirmed and pregnancy was terminated. A focal CNV (of length shorter than 3Mb) has indicated stronger biological relevance. Howe1,2, Alice R. K.M. Sledzinska: None. Arens: None. Mencarelli: None. Genotyping of members of the extended family identified randomisation of the laterality defects in other affected individuals homozygous for the MNS1 alteration, while all unaffected individuals were wild type or heterozygous. When the healthy parents' samples were analyzed the father turned out to have one heterozygous 1677delTA allele, and the mother had two variants - L997F and I1234V (classified as "risk factor" and "CF" alleles respectively). Preliminary results suggest that 2 of the variants appear to be gain-of-function and 6 loss-of-function variants. Pion: None. This enzyme catalyzes the conversion of testosterone to dihydrotestosterone, which is essential for normal differentiation of the external male genitalia and virilization. Ulloa Navas: None. Al Hashmi: None. During follow-up, nodular progression was observed in 26/64 (41%) patients. MET p.(Leu1130Ser) caused a constitutive phosphorylation of ERK protein and induced an abnormal focus formation when transfected into NIH3T3 cell. Mostly, female relatives of patient's are carrier. Dohr: None. Demuynck: None. B.P. González-García: None. Even if ultrasound abnormalities not always suggest a specific syndrome, after a pathogenic CNV is identified a correlation may be possible. We found high precision and recall for SNP calling (>99.5%) and SV calling (>95% and >97% respectively) and median phase block lengths of up to 2.6 Mbp. Each participant was followed-up every six month by telephone interview with a structural questionnaire to obtain the information of their smoking status, smoking quantities, quitting attempt, and major cardiovascular events in subsequent one year. We are now testing whether minicircles containing the correct exon 5 are capable of restoring alpha-1 antitrypsin levels in the genomic-edited organoids. J.R. Rodriguez-Santana: None. First, we established a facial analysis model and showed that facial characteristics of probands with an inherited CHD3 variant significantly overlapped with those of de novo cases. These novel indications for PGT-M will increase the numbers of people who would be candidates for PGT-M. This region's targeted analysis revealed an ~1kb deletion involving in-frame loss of exon 12 of GSN predicted to result in partial deletion and fusion of two gelsolin domains of the protein. Roht: None. Introduction: Synthetic peptides have a wide range of clinical effects. gDNA was extracted from whole blood and the samples were tested for T315I by ddPCR. P17.052.C Bioinformatic NGS data analysis with solida-core Matteo Massidda 1, Gianmauro Cuccuru2, Rossano Atzeni1, Rajesh Pal1,3, Paolo Uva4,5, Giorgio Fotia1 1Centre for Advanced Studies, Research and Development in Sardinia (CRS4), Pula, Italy, 2Albert Ludwigs University, Freiburg, Germany, 3University of Cagliari, Cagliari, Italy, 4IRCCS G. Introduction: Kabuki make-up syndrome (KMS) is a rare condition described by Kuroki and Niikawa in Japanese population in 1981. Santos8, Raquel Maia8, Paula Kjollerstrom8, João Lavinha1, João Gonçalves1, Dezso David1 1Departamento de Genética Humana - Instituto Nacional de Saúde Doutor Ricardo Jorge, Lisboa, Portugal, 2Serviço de Imuno-Hemoterapia, Hospital de S. In 14 individuals we found multiple rare variants in genes causing overlapping phenotypes, which makes these cases difficult to disambiguate. They have an immediate impact on efficiency and on quality, as well as key impacts downstream. Similar results were found for known ER-positive and ER-negative tumours separately. Introduction: here is an interest in finding genetic basis explaining human facial variations because of its impact in different fields such as forensic or biomedical sciences. Appel: A. To clarify the physiological function of PADI4 and PADI2 in RA, we used collagen-induced arthritis (CIA), known as a RA model mouse. This observation supports Brugada type 1 ECG pattern as a possible early sign of an occult structural heart disease, with implications in clinical management and genetic counselling. Deletions of 20p12.1 involving MACROD2 have been associated with ASD according to several studies that preliminarly linked this gene to ASD. We retrospectively studied the genotype-phenotype correlations of 37 cases from 30 families with pathogenic bi-allelic OTOF variations. Kaufmann: None. P05.040.B Pathogenic variants affecting the TB5 domain of fibrillin-1 protein in Marfan syndrome and Geleophysic/Acromicric Dysplasia patients: from tall to shortPauline Arnaud1,2,3, Nadine Hanna1,2,3, Zakaria Mougin3, Geneviève Baujat4, Valérie Drouin-Garraud5, Salima El Chehadeh6, Laurent Gouya2, Sylvie Odent7, Guillaume Jondeau2,3,8, Catherine Boileau1,2,3, Carine Le Goff 3 1AP-HP, Hôpital Bichat, Département de Génétique, Paris, France, 2AP-HP, Hôpital Bichat, CRMR Syndrome de Marfan et pathologies apparentées, Paris, France, 3Université de Paris, LVTS, Inserm U1148, Paris, France, 4AP-HP, Hôpital Necker, Département de Génétique, Paris, France, 5CHU Rouen, Service de Génétique, Rouen, France, 6CHU Strasbourg, Service de Génétique Médicale, Strasbourg, France, 7CHU Rennes, Service de Génétique clinique, Rennes, France, 8AP-HP, Hôpital Bichat, Service de Cardiologie, Paris, France. Using ten-fold cross-validation, our models showed that the area under the receiver operating characteristic curve (AUROC), and the area under the precision-recall curve (AUPR) were on average 0.943 and 0.954, respectively. Materials & Methods: Whole-exome sequencing was performed on two DNA pools, one set up with DNA isolated from 66 AD patients and the other from 100 individuals showing no symptoms of dementia. Further studies to confirm our preliminary findings are warranted. Ricaño-Ponce: None. A.C.H. is supported by BONFOR grant O-149.0123. Introduction: The four most common Y chromosome haplogroups in Turkey are J2, R1b, G and E3b. Exome sequencing revealed the homozygous presence of the pathogenic variant c.1774C>T (p.Arg592Trp) in AARS2. P12.008.C BAP1 germline variations in Finnish patients with malignant mesothelioma Pauliina Repo 1,2, Aleksandra Staskiewicz1,2, Eva Sutinen3, Mikko Rönty4, Tero T. Woman with EPL have shorter telomere that women without miscarriage. Bezerra, Érika C. Drazdauskiene: A. P02.021.B Variants in FZD5 are primarily associated with non-syndromic phenotypes in individuals with ocular coloboma Richard J. Introduction: The GGGGCC (G4C2) repeat expansion in the non-coding region of the C9orf72 gene is the most common genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) (C9ALS/FTD). A subset of the library was integrated and cells were treated with PARP inhibitors. Medvedieva: None. Muriel: None. By performing WGS as a first step this case could have been solved faster and with higher accuracy than the stepwise application of conventional methods. A comprehensive clinical assessment showed that 93% (116/126) of NF1-deleted patients fulfilled the NIH criteria for NF1. Macaya: None. No genetic causes were identified in four patients with partial globozoospermia. This provides further evidence for the pathogenicity of this variant in humans and corroborates the idea that this cohort is ideal to study the mechanisms of clinical heterogeneity. P09.130.C Brain region specific effects on the expression of glucocorticoid receptor-regulated genes Nathalie Gerstner 1,2,3, Anthodesmi Krontira1,3, Janine Knauer-Arloth1,2, Elisabeth B. Rosenberger: None. Menicucci: None. Bacino14, Jill A. Diekmann: None. As a last step, a pathway prioritizing of the "lipid binding" genes was carried out. Notarbartolo: None. Meglič: None. Zhukovskaya3, Svetlana N. In our PRS in cases, we took the summary statistics from a GWAS in CeD (24,269 participants) and tested their association with phenotypes at eight P value thresholds (PT). Ibrahim: None. Gaizevska: None. I.V. Grishchenko: None. We additionally observed abnormal features in a muscle biopsy; this finding warrants further investigation. Povarov, Andrey A. The purpose of this project is to teach the medical genomics concepts essential to the production, analysis, and interpretation of NGS data in the framework of rare disorders and ontogenetic. Patients with multisystem disease of unknown etiology from all over Japan were included in this study. PVs also were found in genes linked to genetics disease not reported in clinical diagnosis of patients, but having distinct clinical manifestations: EXT2 (Exostoses, multiple), NOTCH3 (Cerebral arteriopathy), SOD1 (Amyotrophic lateral sclerosis), CACNA1A (Episodic ataxia) and FGFR3 (Achondroplasia). Interestingly, in the GD/AD patients, the nineteen heterozygous FBN1 mutations all affect the TGFβ-binding protein-like domain 5 (TB5). Introduction: The epigenetic changes are present in all human cancers and associated with genetic alterations to drive a cancer phenotype. Crépin: None. Maksimova: None. Gelderblom: None. Yakut population represents genetic isolates with its unique geographic situation and specific history that have resulted in a relatively higher prevalence of genetic disorders that caused by specific mutation rarely found or cannot be found in other populations. Total RNA was extracted using a Direct-zol RNA Miniprep Plus isolation kit, following the manufacturer's protocol. Grillo: None. Wieczorek30, G. Zitano: None. P14.014.C Frequency of aneuploidy in diploid androgenetic hydatidiform moles Pernille Walbum Kristensen 1,2, Lotte Andreassen3, Marianne Geilswijk3, Thomas Poulsen2, Isa Niemann3, Lone Sunde1,2 1Aalborg University Hospital, Aalborg, Denmark, 2Aarhus University, Aarhus, Denmark, 3Aarhus University Hospital, Aarhus, Denmark. We separated patients in different phenotypic clusters. Introduction: Parkinson's disease (PD) is a widespread disorder of the nervous system. Introduction: Biallelic intronic AAGGG expansion in the RFC1 gene cause cerebellar ataxia, neuropathy, and vestibular areflexia syndrome (CANVAS). Results: ddPCR testing correctly predicted the fetal genotype in 48 cases (32 male, 16 female), with nine of 10 HbSS fetuses correctly identified. P12.147.C Frequency of heterozygous carriage of mutations in the NOTCH signaling pathway genes in clear cell renal cell carcinoma patients & in populations of the Volga-Ural region Elizaveta Ivanova 1, Irina Gilyazova1, Galiya Gimalova1, Adel Izmailov2, Ilnur Sultanov2, Gulshat Gilyazova2, Valentin Pavlov2, Elza Khusnutdinova1 1Institute of Biochemistry and Genetics - Subdivision of the Ufa Federal Research Centre of the Russian Academy of Sciences, Ufa, Russian Federation, 2Bashkir State Medical University, Ufa, Russian Federation. Proband and sister carry a c.475G>C heterozygous mutation of CTLA4 gene, with unknown inheritance. The noncanonical transcripts of the exon 6 of the SCN5A gene is poorly represented in cardiac tissue (gnomAD). Children's Hospital of Lahore Hospital, Lahore, Pakistan, 11Clinical Genetics Department, Human Genetics and Genome Research Division, National Research Centre, Cairo, Egypt, 12Institute of Human Genetics. Nikolaeva: None. UCSC genome browser tool was employed for mapping miRNAs onto collected rCNV regions. Higher coverage and resolution allow more detailed characterization of copy number gains and losses. ILIAD has adopted a data access policy, for requesting access to the data, Governance of the Registry, compliance with applicable legal and regulatory requirements on the use of Personal Data. Aberrant DNA methylation is described as an important contributor in tumorigenesis of cutaneous melanoma. Serman: None. Olesen: None. Department of Pediatrics, Semmelweis University, Budapest, Hungary, 11Heim Pal Children's Hospital Budapest, Budapest, Hungary, 12Department of Neurology, Szent György County Hospital, Szekesfehervar, Hungary. She was followed for growth retardation, and at 4.5 years, she was -3SD for height and weight. Gómez del Pozo5, L. Wojczakowski: None. Ponelle-Chachuat: None. Methods: 302 women with LBC and 1567 without breast cancer were tested for BRCA1/2 PGVs. A subset of 134 LBC affected women who tested negative for BRCA1/2 PGVs underwent extended screening, including: ATM, CDH1, CHEK2, NBN, PALB2, PTEN, RAD50, RAD51D and TP53. Zarca: F. Allele frequencies were aligned with Hardy-Weinberg equation (p>0,05). The study will have practical value in forensics by developing prototype predictive models for specific age-related features based on genetic and epigenetic information, as well as may find practical application in the cosmetic industry by developing products to prevent or slow down phenotypic aging. Prenatal lymphatic anomalies had a prevalence of 25% for increased NT, 19% for pleural effusions and 33% for cystic hygroma in Noonan Syndrome. Novak Andrejčič: None. Trang: None. Bacchelli: None. This is especially true for type-IV-collagen-related nephropathy, covering an intricate phenotypic and genotypic spectrum. We present the clinical manifestations of three non-related individuals with homozygous pathogenic FKBP14 variants: proband 1 (c.587A>G; p.(Asp196Gly)); proband 2 (c.362dupC; p.(Glu122Argfs*7)) and proband 3 (c.2T>G; p.(Met1?)); with experimental data of the variants found in probands 1 and 2. Introduction: In the past two decades, multiple studies have been undertaken to elucidate the genetic cause of the predisposition to mismatch repair (MMR)-proficient nonpolyposis colorectal cancer (CRC); first by genome-wide linkage analysis and, nowadays, using next-generation sequencing techniques. However, those at increased risk of triple-negative (estrogen receptor-negative, progesterone receptor-negative, human epidermal growth factor receptor-negative) breast cancer (TNBC) cannot be identified because predisposition genes for TNBC, other than BRCA1, have not been established. Psoriatic Arthritis (PsA) is a chronic T-cell mediated joint disease occurring in up to 30% of patients with psoriasis vulgaris (PsV). Here, we propose a method (DIVAs) to assess variants combination pathogenicity in support of digenic inheritance. Sistermans1, Martina C. Mutation in the ryanoidine receptor 1 gene (RYR1) is suggest to the common cause. Bianchi: None. Thus, in basal conditions, the differentially expressed genes were mainly involved in transcription and interferon signalling pathways. M.E. AbdelRaouf: None. Shukhov3, Svetlana A. P12.029.A Association of VEGF Haplotypes with Breast cancer risk in North-West Indians Kamlesh Guleria 1, Vasudha Sambyal1, Ruhi Kapahi1, Mridu Manjari2, Meena Sudan3, Manjit Singh Uppal4, Neeti Rajan Singh4 1Department of Human

Genetics, Guru Nanak Dev University, Amritsar, Punjab India, Amritsar, India, 2Department of Pathology, Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, Punjab, India, Amritsar, India, 3Department of Radiotherapy, Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, Punjab, India, Amritsar, India, 4Department of Surgery, Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, Punjab, India, Amritsar, India. Table 1 Distribution of cases and gene Number of cases Total gene number 1 case 192 (59,5%) 2-4 cases 99 (30,6%) 5-15 cases 26 (8,1%) over 15 case (common disorders) (HBB, SMN1, DMD, CFTR, HLA, FMR1) 6 (1,8%) Total 323 Table 2 PGT-M cases perfomed during 2014-2017 PGT-M cases perfomed during 2017-2021 PGT-M number for common disorders 123 (50.2%) 356 (42.4%) Total number of PGT-M 245 840 L. P09.054.C FKBP5 in First-Episode Psychosis: Insights from a Greek population sample Daniela Theodoridou 1, Alexandra Polyzou2, Angeliki Maria Vlaikou3,4, Michaela D. Variant laboratory database or VCF files were queried by genomic positions of Genome Alert!'s clinically potential variant selection. In addition, somatic TP53 mutations were observed in 73% of tumours. So far, four PPCD1 families have been described, each with an activating variant in a distinct part of the promotor region of OVOL2. Introduction: Retinal dystrophies (RD) are a group of inherited retinal disorders characterized by progressive photoreceptors and pigment epithelial cells dysfunction causing severe visual loss and eventual blindness. Smith4, Andrew Dubowsky2, David Lawrence5, Karin Kassahn6, Sui Yu1, Kathie Friend1 1SA Pathology (Women's and Children's Hospital), North Adelaide, Australia, 2SA Pathology (Flinders Medical Centre), Bedford Park, Australia, 3Paediatric and Reproductive Genetics Unit (Women's and Children's Hospital), North Adelaide, Australia, 4Neurology (Women's and Children's Hospital), North Adelaide, Australia, 5CCB ACRF Cancer Genomics Facility, Adelaide, Australia, 6SA Pathology (Technology Advancement Unit), Adelaide, Australia. Karakurt: None. Several genes, including FAM136A, DTNA, PRKCB or SEMA3D have been found in autosomal dominant familial Meniere's disease (FMD). P01.015.C Chromosomal abnormalities in prenataly identified cases with amniocentesis from south of Turkey Ayfer Pazarbasi 1, Davut Alptekin1, Sabriye Kocaturk-Sel1, Inayet N. Sobreira: None. Introduction: Lynch Syndrome (LS) is a form of hereditary colorectal cancer (CRC), caused by germline variants in DNA mismatch repair (MMR) genes. Conclusions: Here, we present a large family presenting two distinct RD-phenotypes and at least three mutations segregating across three generations. Moreover, this study suggests that microcephaly, reduced sensitivity to pain, cleft lip/palate, gastrointestinal symptoms and ophthalmological symptoms are part of the phenotypic spectrum. Kegler: None. Alterations at any stage can result in a wide range of neurodevelopmental disorders (NDDs), that are a common cause of developmental delay, intellectual disability, and epilepsy. Pregnancies with T8M in CVS and no additional numerical chromosomal aberrations were included. Krasauskas: None. Conclusions: The variant found in our patients was c.5811dupT; p.Val1938fs is the novel variant previously not reported in the literature. Materials and Methods: Utilizing teachings of human genetics, the CD8A CSR messenger ribonucleic acid (mRNA) was re-coded to carry both a cure for COVID-19 and an updated vaccine. All tumors (Wilms tumors, glioblastoma and lymphomas, n = 8) and non-neoplastic samples (n = 19) from the three CMMRD patients showed a positive hs-MSI score (>4.576). Izhevskaya: None. Moreover, we also identified compound heterozygous variants in MUTYH gene: the first variant, a known protein truncating variant associated with colorectal cancer, c.1354G>T; p.Glu452* and the second variant is a novel c.116C>T; p.Ala39Val variant. P11.044.B A rare duplication in 8p11 region Marta Souto 1, Pedro Botelho1, Márcia Martins2, Osvaldo Moutinho3, Rosário Pinto Leite1 1Laboratório de Genética, Centro Hospitalar Trás-os-Montes e Alto Douro, Vila Real, Portugal, 2Consulta de Genética, Centro Hospitalar de Trás-os-Montes e Alto Douro, Vila Real, Portugal, 3Serviço de Ginecologia/Obstetrícia, Centro Hospitalar Trás-os-Montes e Alto Douro, Vila Real, Portugal. Margalit: None. Methods: The study was carried out on a patient with a hypermobile type of EDS. The identification of PitNET derived miRNAs in plasma remains challenging due to tumor volume and miRNA dilution within blood. Clinical validity of ddPCR assays for residual disease detection was confirmed in 19 samples of R0 resected CRC patients, as ctDNA detection was in line with clinical evidence: In 5/19 patients, residual disease was detected. Bustamante: None. We examined that the clinical disease score of CIA mimce and expression levels of Padi genes in PADI2−/− CIA mice. Thus, we found population-specific pathways of PE: these are the processes of immune response for Indo-Europeans and the processes of ligand-receptor interaction for Mongoloids. Here, we provide estimates of the heritability of grey-matter volume in 74 regions of interest (ROIs) and map genetic correlations between these ROIs and behavioural outcomes. P22.031.B Tele-consultations at the patient's home in genetics: an expected practice, boosted by the pandemic Allan Lançon 1, Amandine Beaudouin1, Estelle Petit2, Geoffrey Bertolone1,2, Amandine Baurand1,2, Salima El Chehadeh3, Claire Kastner3, Laurine Tempé3, Christelle Cabrol4, Chloé Trouvé4, Elise Boucher Brischoux4, Mélanie Berard5, Alexia Burtin5, Bruno Leheup5, Mathilde Renaud5, Axelle Rivière5, Céline Poirier6, Marta Spodenkiewick6, Lola Lissy6, Caroline Sawka1,2, Marion Robert1,2, Christel Thauvin-Robinet2, Elodie Gautier2, Sophie Nambot1,2, Juliette Piard4, Martine Doco-Fenzy6, Elise Schaefer3, Laetitia Lambert5, Laurence Faivre1,2 1Service d'oncogénétique, Centre Georges François Leclerc, Dijon, France, 2Service de Génétique, Centre Hospitalier Universitaire, Dijon, France, 3Service de Génétique Médicale, Hôpitaux Universitaires de Strasbourg, Institut de Génétique Médicale d'Alsace, Strasbourg, France, 4Centre de Génétique Humaine, Centre Hospitalier Universitaire, Besançon, France, 5Service de Génétique Clinique, Centre Hospitalier Universitaire, Nancy, France, 6Service de Génétique, Centre Hospitalier Universitaire, Reims, France. Periyasamy: None. Genesio: None. Bellazzi2, Tania Castro1, Viviana R. Experiments were performed using equipment of Center for collective use of the North-Eastern Federal University. Alves: None. Our approach provides novel insights of use in training practitioners. This study determines an updated PPV for triploidy using SNP-based NIPT, following the removal of known viable twin gestations. Onset of the disease occurred at the age of 36 with episodes of hyper- and hypo-glycaemia. Visconti: None. Conclusions: We report two novel pathogenic variants in SOX4 abolishing the transcriptional activation of SOX4 in vitro. W.A.G. van Zelst-Stams: None. The following dysmorphic features were noted: facial coarseness was minimal - thick eyebrows, mild micrognatia, long broad philtrum, nose with bulbous tip and anteverted nostrils. Here, we studied the frequency of pathogenic germline variants (PGVs) in an extended panel of genes in women affected with LBC. To address these challenges, two novel microfluidic technologies were integrated for efficient DNA extraction and PCR-free WGS library production. D.D. Khukhareva: None. ResultsCase 1: A 34-years-old pregnant woman was referred due to prenatal ultrasound of frontal antlers fusion, suspicion of holoprosencephaly, clubhand and facial proboscis. Regulatory variants were then annotated using ANNOVAR v (2018-04-16) to identify those with potential effects on RIG-1 expression, splicing and/or function. Additionally our study emphasizes that unexplained phenotypes may result from the occurrence of pathogenic variants of two or more genetic disorders in the same patient. The serious game is designed alongside the help of parents and specialists and it allows medical practitioners to reinforce their knowledge in the diagnostic strategies and care of neurodevelopmental disorders in an interactive way. Conclusion: The creation of a collection of samples of pregnant women is a significant groundwork for future fundamental and applied research in various fields of biomedicine. A fingerprint represents the statistical associations arising from studying ~1300 quantitative traits in the UK Biobank 300K exomes. P03.045.A Contribution of a non-coding variant in autosomal recessive ACTG2-related visceral myopathy identified by whole-genome sequencing Mari Mori 1,2, Kristen V. Gochuico, Alisa M. We aimed to evaluate possible associations of NFE2L2 rs10183914, rs35652124, HMOX1 rs2071746, TXNRD2 rs1139793 SNPs with the early-stage BC clinicopathological characteristics and survival. Schot: None. Here, we present a strategy to characterize the breakpoints by Whole Genome Sequencing (WGS) on an apparently balanced pericentric inversion X (p22.13-q27.3), maternally inherited, in a child with syndromic bilateral cataracts and its implications in the phenotype. Identifying the subtype with molecular studies is important for patient's follow-up. Present data show that several factors- both environmental and genetic - influence concomitant sensory declines. Briansó: A. Srebniak1, Hennie T. Seneca: None. Patients with SOPH syndrome were characterized by low percentage and number of CD16+CD56+ NK cells and slightly lower levels of CD19+ B cells. Voinova2, Alexander K. P11.051.A A case of ESCO2 spectrum disorder without limb reduction defects Sofía M. Here we report the sole and combined effect of valproic acid (VPA), a class I selective HDAC inhibitor, and hydralazine (HYD), a DNA methyltransferase inhibitor, drugs over the expression of pluripotency genes in adult and newborn fibroblasts. Almogren: None. Hernandez-Ferrer: None. S.R.B. Heymans: None. Feben: None. Most received their genetic diagnosis in the post-neonatal period. van Bever: None. Alastalo: A. Confidence intervals were computed by bootstrap. Gonye: A. Conclusion: Our results do not support additional benefit for CAD prediction by adding several independent GRSs in addition to a CAD GRS alone. Dinopoulos: None. Variants of interest were confirmed by Sanger Sequencing. Results: We screened 6485 publications and included: 61 HTRA1 (126 individuals), 35 TREX1 (123 individuals), 100 ADA2 (346 individuals), and 5 CTSA (14 individuals). Half of the respondents avoided more than 1.5 hours of transport and 69% avoided taking a day off. Voices and I-poems were used to illustrate these themes. Souaid: A. Overall RRM uptake was 57.9% and RRSO uptake was 78.6%. Materials and methods: During diagnostic procedure analysis of karyotyping, MLPA test (P-245), comparative genomic hybridization to microarray (aCGH) study and sequencing a panel of 372 genes (NGS) correlated with short stature, dysmorphic features and mental retardation were performed. An increased nuchal translucency motivated a second prenatal diagnosis, showing an accumulation of dermatan sulfate and chondroitin sulfate. Non-HDGC-families presented a truncating variant cluster in CTNNA1 last exon. Chatziandreou: None. Ordonez-Herrera: A. N.A. Carvalho: None. Boutin: None. For the analyzed period, there is an increase in T21 total prevalence: from 18,30 in 2011 it increased to 23,33 in 2019. Variant reads accounted for 33% and 92% of total reads in the nevus and tumor, respectively, supporting the occurrence of a second event involving the gene specifically arising in the latter. Kornienko1 1St.-Petersburg State Pediatric Medical University, St.-Petersburg, Russian Federation, 2N.N. Petrov Institute of Oncology, St.-Petersburg, Russian Federation. Bilska: None. This poster will demonstrate the utility of this powerful diagnostic tool as we review the initial phase of its introduction into service. Kamien: None. The diagnostic and clinical utility is verified by a diagnostic rate of 46%. P09.142.C Genetic variation spectrum of ATP7B in a cohort of 113 patients with Wilson disease João Parente Freixo 1, Ana Lopes1, Rita Bastos-Ferreira1, Henedina Antunes2,3,4, Ermelinda Santos Silva5, Jorge Sequeiros1, Marina Magalhães6, Jorge Oliveira1 1CGPP - Centro de Genética Preditiva e Preventiva, IBMC - Instituto de Biologia Molecular e Celular, i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal, 2Pediatric Gastroenterology Hepatology and Nutrition Unit, Hospital de Braga, Braga, Portugal, 32CA – Clinical Academic Center, Braga, Portugal, 4ICVS - Life and Health Sciences Research Institute, School of Medicine, University of Minho, Braga, Portugal, 5Unidade de Gastroenterologia Pediátrica, Serviço de Pediatria, Centro Materno-Infantil do Norte, Centro Hospitalar Universitário do Porto, Porto, Portugal, 6Serviço de Neurologia, Centro Hospitalar Universitário do Porto, Porto, Portugal. Kremer: None. Our functional assays show that the mechanism underlining ARFGEF1-related conditions is consistent with haploinsufficiency. Riess: None. The c.1073+5G>A variant in the PRPF31 gene was homozygous in two RP patients. We also carried out genome-wide DNA methylation analysis. Balla: None. Howell3,4,6, Anthony Howell3,4, Fiona Lalloo2, William G. The study objective was to collect, analyze, and uniformly summarize all published GALNS gene variants, thus updating the previous review (Morrone A. Fenwick: None. Santorelli: None. In this retrospective study we evaluate the yield of gene-panel CL/P testing. E.F. Mikhailidi: None. Castro: None. The growth arrest specific 2 (Gas2)-related (GAR) domain of MACF1 interacts with microtubules and dominant variants affecting the GAR domain result in a brain malformation involving a predominant posterior lissencephaly and reduced or absent pontine crossing fibers resulting in a W-shaped hypoplastic brainstem. Dubourg: None. All three novel variants were evaluated as likely pathogenic. Sachdev: None. Clinical genetics services have adapted to the ongoing challenges of social distancing and redeployment whilst balancing the safety of colleagues and patients. However, COL12A1 is not deleted in our case, suggesting a key role for other genes, such as COL9A1 and COL19A1, in the etiology of these problems. P11.110.D Truncating mutations in MAGEL2 cause alterations in Aβ1-40 levels and gene expression in fibroblasts Laura Castilla-Vallmanya 1,2, Mónica Centeno-Pla1,2, Héctor Franco-Valls1,2, Aina Prat-Planas1,2, Elena Rojano3, Pedro Seoane3,2, James R. Ruiz-Perez: None. He was the third child of healthy non-consanguineous parents. Radhakrishnan: None. Funding: Estonian Research Council grant PRG471 S. DNA extraction, mtDNA sequencing and mtDNAcn were performed on tumors and matched adjacent-normal tissues. P11.027.A A new ocular phenotype in cardiofaciocutaneous syndrome Maria Tessitore 1, Giulia Abbinante1, Mariateresa Falco2, Flavio Gallo1, Carnem Plaitano3, Dario Di Salvio4, Adriano Magli1, Daniela Melis1 1Scuola Medica Salernitana, University of Salerno, Salerno, Italy, 2Pediatric Unit San Giovanni di Dio e Ruggi d'Aragona University Hospital, Salerno, Italy, 33. Mattina: None. Atrophic scarring and easy bruising were less frequent in hEDs patients (p T (p.Pro380Ser) is not available in the ExAc, according to in silico tools this is also VUS. Szczepanik: None. Children with at least one risk allele for SNP rs9939609-FTO showed more frequent episodes of loss of control over food and chose foods rich in energy. Nelson9, UCLA California Center for Rare Disease9, Pia Zacher10, Rami Abou Jamra10, Chiara Klöckner10, Julie McGaughran11, Jürgen Kohlhase12, Sarah Schuhmann1, Ellen Moran13, John Pappas13, Annick Raas-Rothschild14, Maria J. Wieczorek: None. Fiévet: None. Conclusions: Our results demonstrate the successful generation of hiPSC-based in vitro models mimicking the disease phenotypes, proving a valuable system for molecular investigations and drug development. Bukowska-Olech: None. D.G. Zheglo: None. Krawitz1 1Institute for Genomic Statistics and Bioinformatics, University Hospital, Bonn, Germany, 2Division of Newborn Medicine Division of Genetics and Genomics Boston Children's Hospital, Boston, MA, USA, 3Center for Pediatrics, Devision for Neuropediatrics, University Hospital, Bonn, Germany, 4Department of Pediatrics, Cedars-Sinai Medical Center, Los Angeles, CA, USA, 5Centre for Mendelian Genomics, Clinical Institute of Genomic Medicine, UMC Ljubljana, Ljubljana, Slovenia, 6Department of Pediatrics and Medicine, Columbia University Irving Medical Center, New York, NY, USA, 7GeneDx, Gaithersburg, MD, USA. Stevanin: None. R.M. Martin: None. El-Kamah National Research Centre, Cairo, Egypt. Barbance: None. P16.036.C Identification of structural variation in constitutional disorders by optical genome mapping Andy Wing Chun Pang, Alex Hastie, Alka Chaubey Bionano Genomics, San Diego, CA, USA. Bagnasco: None. Ocular involvement occurs in the majority of individuals and include: strabismus, refractive errors, nystagmus, ptosis, and optic nerve hypoplasia. An important downregulated miRNA is represented by miR-185 a biomarker of therapy response targeting MAPK signalling. 20-15-00262). Roofthooft6, Patrick Deelen1,4, Conny M. Mekov: None. Stolk1, Sabine Otten1 1University of Groningen, University Medical Center Groningen, Groningen, Netherlands, 2University of Southampton, Southampton General Hospital, Southampton, United Kingdom. In a training subset (50%, N = 26,127), we identified the risk factors significantly associated with CAD using Multivariable Cox regression to build three scores, Sc1 including sex, age and traditional risk factors, Sc2 including Sc1 and a GRS for CAD, and Sc3 including Sc2, and 26 additional GRSs for traditional and electrocardiogram risk factors. Additional findings were seizures (24%), minor structural brain abnormalities (24%) and scoliosis (19%). SNP-array and FISH analysis showed that the mildly affected mother harbors the same 6q27 deletion. Results: We created libraries using the standard workflow and all libraries passed the quality thresholds. Benavente: None. The genotyping service was performed at CEGEN-PRB3-ISCIII, supported by grant PT17/0019, of the PE I+D+i 2013-2016, funded by ISCIII and FEDER. Cosegregation analysis didn´t allow to confirm the pathogenicity of the 6 VUS with high probability of pathogenicity. This report demonstrates that NBS for CH is feasible and effective in preventing the disease burden. The biological mechanism underlying this effect is unclear but is likely to be independent of adult BMI. Farooq: None. Davydiuk: None. Although mitochondrial sequence alteration was investigated in the pathological context, little is known about the effect of its variation among the population on phenotypic traits. Byers: None. Maj: None. P17.026.A A Flexible and Shared Information Fine-mapping Approach with an application to 33 cardiometabolic traits from a Ugandan cohort Nicolás J. Kotur: None. Conclusions: Genetic disorders were suspected in 13% of the cohort, but only confirmed in 5%. After genetic counseling the parents opted to terminate the pregnancy. The InSiGHT-ClinGen effort might serve as a model for other variant interpretation initiatives. Braakman22, Martin Haeusler23, Miriam Elbracht24, David Sternman25, Ulvi Vaher26, Thomas Smol27, Joanna Kennedy28, Karl Martin Klein29, Billie Au30, Kimberly Smyth31, Thomas Morgan32, Malin Dewenter33, Argirios Dinopoulos34, Damien Lederer35, Vivian Liao36, Philip K. Together, our findings show that biallelic loss-of-function variants in MAPKAPK5 result in a severe developmental disorder and demonstrate a key role of this gene in human brain, heart, and limb development. Tuupanen: A. Doco-Fenzy: None. Material and methods: The new features have been implemented on the RD-Connect GPAP, which processes and indexes pseudonymised genome-phenome data submitted by partners from Solve-RD and EJP-RD, among others. 4 variants(M680I(G/A), P369S, 1692del and A744S) were not detected. Conclusions: SHS is a distinct neurodevelopmental disorder with multiple congenital anomalies, and the identification of additional cases increases the current understanding of its clinical spectrum. To benchmark the current capacity of these professionals to deliver genomic healthcare, an online survey (available in English and Welsh) was developed. P02.036.A Genetics of Inherited Retinal Degenerations in Icelandic patients Daniel A. Imrich: None. El Mabrouk: None. Within this region, genes involved in Immune Disorders can be identified, among them, CTLA4. And, MSH2-Gly322Asp was significantly associated with HER2-positivity(p = 0.028) in Tanzanian BC patients. Based on the adapted allele frequency thresholds, it is likely that in particular a considerable portion of VUS can be reclassified as (likely) benign. Al-Abdulwahed: None. Diagnosis is important for management and genetic counselling. For example, summary statistics were available for 58% of ovarian cancer studies published since 2017, compared to only 6% of leukaemia studies. T.B. Haack: None. Four patients had intrauterine growth restriction. Crosbie: None. P20.011.B Disease interpretation of non-coding genomic elements with the GeneCards Suite Ruth Barshir 1, Simon Fishilevich1, Tsippi Iny-Stein1, Ofer Zelig2, Yaron Guan-Golan2, Marilyn Safran1, Doron Lancet1 1Weizmann Institute of Science, Rehovot, Israel, 2LifeMap Sciences Inc, Alameda, CA, USA. AlGhamdi: None. In this study the genetic background of adult onset mitochondrial disorders were investigated in Hungarian patients. We also inserted a 3xFLAG tag at the N-terminus of TTBK2. Borg: None. Some individuals also present with cardiac malformations as well as mild to moderate mental retardation. Regarding the inheritance, 40% were autosomic dominant, 36% were X-linked, 20% were autosomic recessive and 4% were imprinting mutations. Conclusion: The performed functional analysis allowed us to characterize the splicing outcome for 14 PA variants and reclassify them according to ACMG/AMP guidelines. Materials and methods: Eight patients with differential diagnosis Marfan and Marfan like syndromes and 1 patient with Ehlers-Danlos were directed for targeted next generation sequencing (NGS) in Molecular medicine center in the period 2019-2020 year. P16.005.D Congenital anomalies and genetic disorders in neonates and infants: a single-center observational cohort study Abderrahim Marouane 1, Richelle A. Ilieva, E. Marais: A. Materials and Methods: HepG2 cells were treated with different concentrations and combinations of sorafenib, VPA and metformin for 48 h to evaluate viability with alamar blue assay, migration with a wound healing assays, and angiogenic potential by RT-qPCR assays with Taqman probes spanning on VEGF-A and GAPDH genes. Materials and Methods: Current scRNA-Seq methods are not easily adopted in the virology lab as they are expensive, require complex instrumentation and consumables, and hence can be challenging to implement in a laboratory with limited resources and accessibility. Introduction: Initial step of PGT-M is the detection of causative mutation. CIBERER, ISCIII, Madrid, Spain., Madrid, Spain. Consultant/Advisory Board; Modest; Sanofi-Genzyme, Novartis, Servier, Biogen. We have used data from 6144 trios that have undergone diagnostic evaluation as part of the Genomics England 100,000 Genomes Project, including 2715 trios analysed with an advanced Dn identification pipeline. P25.009.D Analysis of the distribution of the rs657152 and rs11385942 associated with the severe course of COVID-19 in the populations of Northern Eurasia Natalia V. WGS was performed and analyzed with our software for routine NGS diagnostics (GensearchNGS, Phenosystems). After 1 month, RNA was isolated from pancreas and after reverse transcription, the following genes were analyzed by real-time PCR: INS, GCK, ABCC8 and KCNJ11. Variants in EGFR were predominantly in-frame deletions in exon 19 (37%) and L858R (32%). Belda: None. J.R.B. Perry: None. Logistic regressions were performed on pPRS per p-value-cutoff and library. We aim to assess the causality between physical activities, sedentary behavior and body mass index (BMI) in adults by bidirectional Mendelian randomization analyses. Introduction: The LPA gene encodes apolipoprotein(a) and is the main genetic regulator of lipoprotein(a) [Lp(a)] concentrations. The study of the somatic mutations in human tumors has led to the characterization of a diverse set of mechanisms which can create multiple genetic changes in a single event. MPS IVA is a clinically heterogeneous disorder, whose presentation varies from a classical rapidly progressing to a nonclassical form. Lam: A. Two different novel frameshift pathogenic variants and three other previously reported frameshift, nonsense and splicing pathogenic variants were identified. P22.025.D MOOC on Bioinformatics in Genomic Medicine (BiG MOOC) Evan Gouy 1,2, Kevin Yauy3,4, Anne-Sophie Denommé-Pichon5,6, Emanuelle Génin7, François Lecoquierre8, Alban Lermine9, Robert Olaso10, Jean-François Deleuze10, Sacha Schutz11, Marie de Tayrac12, Aurélien Trimouille13, Guillaume Collet14, Xavier Desplas2, Fabien Hobart15, Amodsen Chotia2, Agata Urbanczyk16, Olivier Palombi16, Pascal Pujol17, David Geneviève18, Laurence Faivre19,5, Damien Sanlaville1, Yannis Duffourd5,6, Andrew Green20, Janna Kenny20, Sally-Ann Lynch20, Sarah Wedderburn21, Helena Carley22, Anne Hugon23, Sarra Selatnia23, Klea Vyshka23,24, ERN-ITHACA Executive Committee, Julien Thevenon25, Alain Verloes23,26 1Service de génétique, Hospices Civils de Lyon, Bron, France, 2Centre de Recherche Interdisciplinaire, Paris, France, 3Institute of Advanced Biosciences, Centre de recherche UGA, Inserm U 1209, CNRS UMR 5309, Grenoble, France, 4SeqOne Genomics, Montpellier, France, 5Unité Fonctionnelle Innovation en Diagnostic génomique des maladies rares, FHU-TRANSLAD, CHU de Dijon, Dijon, France, 6UMR1231 GAD, Inserm – Université de Bourgogne Franche-Comté, Dijon, France, 7UMR 1078, Inserm, Brest, France, 8Laboratoire de génétique, CHU de Rouen, Rouen, France, 9MOABI-APHP, Paris, France, 10CNRGH, CEA, Evry, France, 11Laboratoire de Génétique, CHU de Brest, Brest, France, 12Laboratoire de Bioinformatique et Génétique Computationnelle, Service de Génétique Moléculaire et Génomique, CHU de Rennes, Rennes, France, 13Service de génétique médicale, CHU de Bordeaux, Bordeaux, France, 14Réseau BioInfoDiag INCa, Rennes, France, 15Nipédu, Nipcast, Paris, France, 16Université Numérique de la Santé et du Sport, Grenoble, France, 17Unité d'oncogénétique, Service de Génétique Clinique, CHU de Montpellier, Montpellier, France, 18Service de Génétique Clinique, CHU de Montpellier, Montpellier, France, 19Centre de Référence maladies rares "Anomalies du développement et syndromes malformatifs", centre de génétique, FHU-TRANSLAD, CHU de Dijon, Dijon, France, 20Department of Clinical Genetics, Temple Street Children's University Hospital, Dublin, Ireland, 21NHS Greater Glasgow and Clyde, Glasgow, United Kingdom, 22South West Thames Regional Genetics Service, London, United Kingdom, 23Dept. The analysis was boosted with clinically relevant deep intronic variants and a proprietary copy number variation (CNV) analysis method for exon-level CNVs. Variant interpretation followed ACMG guidelines. Baert-Desurmont: None. Materials and methods: Total RNA was isolated from tissue samples of ectopic endometrium of 30 patients with endometriosis and healthy endometrium of 15 controls (miRNeasy-MiniKit,Qiagen). Jaskiewicz: None. T.S. Matis: None. Four full-length DMBT1 transcripts sequenced using a single sequencing read (6.7kb) showed a SRCR-domain number consistent with the genotype. Guterman Ram: None. Cytokines are proteins and glycoproteins implicated in innate and acquired immunity, embryogenesis, hematopoiesis, inflammation and regeneration processes, and proliferation. Snijders Blok: None. Vicente: None. The performance of this miRNA-assigned CMS-classifier (CMS-miRaCl) was validated in two independent data sets. Conclusion: We demonstrated population/ethnic difference in the frequency of previously announced rare genetic variants, suggesting higher contribution risk effect of GCGR to DM. Fabio: None. All 27 patients presented with sudden infant death and all patients with a 46,XY karyotype had DSD. Currently, clinical and germline WES data from 294 cases are analysed. Genotyping of targeted SNPs: A223G (LEPR), A23525T (FTO), C786T (NOS3), C634G (VEGFA) were detected by RT-PCR. Whole-exome sequencing (WES) data were obtained from six individuals belonging to the same family. Al-Harazi: None. H.O. Aldeeb: None. Employment (full or part-time); Modest; CENTOGENE AG. Parental karyotypes were normal indicating that this rearrangement occurred de novo. The majority of infected individuals have experienced no or only mild symptoms, ranging from fully asymptomatic cases to mild pneumonic disease. Monoallelic MLH1 germline promoter methylation was found to completely abolish mRNA expression from the methylated allele. At 22 months, she presented immunodeficiency, complicated with recurrent infections/intractable diarrhea and anemia. Groups 3, 5 & 6 from couples with no known fertility issues all have lower incidences. Our findings provide evidence that EVs with specific surface proteins are genetically and phenotypically associated with obesity, guiding future EV biomarker discovery. Previously, we systematically analyzed the experimentally identified mRNA-microRNA duplex regions from available CLASH and CLIP datasets. They also narrow the list of these putative candidate human and bovine genes. Tsirligkani: None. One patient suffered an intracranial aneurysm with vascular complications in 3 relatives including thoracic and abdominal aortic aneurism and dissection and intracranial aneurysm rupture. This work was supported by the Russian Foundation for Basic Research (grants no. Duban-Bedu: None. P12.113.A Extended gene panel testing in lobular breast cancer Elke M. Karyotype, chromosomal microarray analysis (CMA) and BWS molecular testing (methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) analysis of 11p15 BWS critical region) were performed after amniocentesis. The muscle biopsy analysis was consistent with muscular dystrophy. Ownership Interest (stock, stock options, patent or other intellectual property); Modest; AstraZeneca. P19.020.D Exome sequencingof 1293patientsin Russia: new knowledge aboutthestructureofinherited diseases in Russia Oxana Ryzhkova, Olga Mironovich, Polina Gundorova, Anna Orlova, Tatiana Cherevatova, Alyona Chukhrova, Viktoria Zabnenkova, Olga Schagina, Varvara Kadnikova, Nailya Galeeva, Alexander Poliakov Research Centre for Medical Genetic, Moscow, Russian Federation. Regarding hyperplastic polyps, there was no significant difference. Introduction: Spinocerebellar ataxias (SCAs) are a group of genetically heterogeneous, dominantly inherited ataxias. Conclusions: This study inspected how medical students handled uncertainties from prenatal ES, showing that more uncertain results are less likely to be reported. Fors: None. Supported by: VEGA 0211/18, VEGA 0131/21 T. Murphy: None. Sincic: None. Clinical evaluation included: echocardiography, cardiovascular magnetic resonance, NYHA class, ECG, 24-hour Holter ECG and family history. Two 55 y.o. twins were suspected for adult form of NPC, based on clinical and biochemical symptoms and were referred for a genetic testing. Results: Analytical performance was evaluated on overall call rate (>99%) and concordance to independent genotypes (>99.8% vs 1000 Genomes Project Phase III). These genes cluster in GO terms related to cell cycle and cell division (p A, results in the substitution of a conserved cysteine at position 148 with a serine (p.Cys148Ser, NM_213653.3). Copy Number Variation (CNV) were evaluated using DecoN algorism and MLPA-P215-B3-EXT-Kit. Vears 1,2,3, Marjolein Kriek4, Koen L. Belur: None. The presence of CNVs on chromosome 1, the largest human chromosome, is a known cause of morbidity. Well-characterized variants were identifiable: 1) G-to-A transition in CYP2C19 exon5 in GM12878, 2) F508 deletion mutation in CTFR in GM07339, 3) R553X mutation in GM07461. Begtrup: None. At date about 100 mutations have been reported in a few families. Allele and genotype frequencies were compared between 314 individuals aged 85+ and 97 individuals aged 20-35 years. Tüttelmann: None. Clinical presentation of LIWAS in the neonatal period could be similar to MMIHS with bowel and urinary bladder problems being dominant clinical signs. On the other hand, P&Cs addressed problems of infantilism, not adequate attitude towards adolescents, no independence, sexuality as taboo, lack of self-deciding, including range of medical care needed. Rukova: None. Hommersom 1,2, T. P09.079.D DNA methylation pattern of gene promoters of MB-COMT, DRD2, and NR3C1 in Turkish patients diagnosed with schizophrenia Hasan Mervan Aytac 1, Yasemin Oyaci2, Mustafa Pehlivan3, Sacide Pehlivan2 1Psychiatry Unit, Malazgirt State Hospital, Mus, Turkey, 2Department of Medical Biology, Istanbul Faculty of Medicine, Istanbul University, Turkey, Istanbul, Turkey, 3Department of Hematology, Gaziantep University, Faculty of Medicine, Gaziantep, Turkey, Gaziantep, Turkey. By molecular modelling, the Asn83Lys modification induces a significant perturbation of the protein structure, altering signal transduction or small-molecule transport by modulating the length of TMDs. Conclusion: We described a novel Asn83Lys mutation in NIPA1 in a patient displaying the chief phenotypical characteristics of SPG6. Employment (full or part-time); Modest; This author is the founder and CEO of Consent MD. SenGupta: None. Therefore, the search for new fusion genes is very important for a personalized approach in medicine. These results highlight the idea of genetic continuum for different cardiomyopathy phenotypes. Frequencies of associated alleles and genotypes were compared with 1000 Genomes project data. coli isolates were obtained aleatory from urocultures in a Portuguese hospital, during June 2017-July 2018. Owaidah: None. Gzgzyan1, Igor Yu. Kogan1, Vladislav S. Exome sequencing greatly increased the diagnostic yield of genetic forms of NDDs, allowing the identification of variations in hundreds of genes. W.E. Ek: None. Ludwig3, Öznur Yilmaz2, Tobias Lindenberg2, Ute Moog7, Alina C. Patients were tested using an NGS custom panel comprising the four aforementioned genes. Materials and Methods: We identified rare diseases using Orphadata (orientdb version) and categorized them into 3 categories based on prevalence, borderline-common (1-9 cases per 10,000), rare (1-9 cases per 100,000 and 1,000,000) and ultra-rare (less than 1 case per 1,000,000). It is able to annotate any small DNA variant (substitutions or small insertions/deletions), either exonic or intronic, lying within 18,500 human genes. DNA samples were analyzed by exome sequencing (Agilent kit) on Illumina platforms. S.B. Sousa: None. We increase our knowledge on the fetal phenotype caused by the aberrant cell line which is only rarely reported. Methods: ddPCR assays were designed for 24 pregnancies at risk of X-linked recessive (14), X-linked dominant (1), autosomal dominant (7) and autosomal recessive (2) conditions. P11.049.C Mandibulofacial Dysostosis with Microcephaly due to EFTUD2 gene mutation. Conclusions: The use of a complex of modern cytogenetic methods, FISH with DNA probes, or SHANK3 gene sequencing can significantly increase the number of diagnosed cases of genetically determined mental retardation and increase the effectiveness of preventive measures. The Se and Sp was 34% and 99%. Costeas: None. Poláková: None. In this study we re-evaluated whether BLK, KLF11 and PAX4 cause MODY. I.C. Adolf: None. The present study aims to explore the attitudes of both Bulgarian genetic counselors and random participants to its usage.We conducted an online survey among 200 randomly selected people, who have not visited a genetic counselor, and 19 genetic counselors from Bulgaria in January 2021. Genetic counselling has been dealing with outcomes of tests that are not related to the initial indication since conventional karyotyping is used. When they are acting in opposite directions, observed effects are underestimated for all overlaps because the three sources of biases are towards the null. Ward: None. Rahikkala: None. Rivera-Barahona: None. Mei: None. Methods: Extensive literature review was conducted to collect data about pathogenic rCNVs associated with CAKUT. The T allele and the TT genotype of rs2165241 presented at significantly higher frequencies in XFS patients (p = 0.00473, OR = 2.10; p = 0.00001, OR = 4.49, respectively). Bloch-zupan: None. Results: We could not confirm the previously detected association between the CYLD gene and ALS. Mazurkiewicz: None. A.V. Marakhonov: None. As a collaborative effort, an InSiGHT-ClinGen Hereditary Colon Cancer/Polyposis VCEP is constituted in the ClinGen Hereditary Cancer Clinical Domain. The variant p.Pro543Leu was found in three heterozygous individuals (AF = 0,00148) that share a common haplotype. The application imports data into a local relational database wherefrom complex filter-queries can be built either from the intuitive GUI or using a Domain Specific Language (DSL). There is 100% detection for all the samples (N = 20) that spiked-in 1 copy/uL heat-inactivated virus. Around 70—80% of all epileptic cases are caused by genetic mutations. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Modest; Russian Science Foundation. Panovská: None. Here, we examine the time of transcription of the candidate genes from human chromosome 19 and its ortholog, bovine chromosome 7, using single cell RNA sequence data from preimplantation human and qRT-PCR data from bovine embryos. Our results show that applying MR to infectious disease studies can help verify the risk factors that are truly associated with serostatus, especially when traditional epidemiological studies provide opposing results. Utkus: None. Eligible patients must have one or more of: skeletal abnormalities suggestive of SD, short stature, disproportionate growth, dysmorphic facial features or other signs suggestive of SD. After holidays, f-SatIII content in DNA decreases, and the TR content increases. It is important to bear in mind there was no one method that suited all patients, and, consequently, we need to remain patient focused in our decision making. Vázquez-Rodríguez3, Manuel Hermida-Prieto1 1Cardiology Research Group, Instituto de Investigación Biomédica de A Coruña (INIBIC)-CHUAC-UDC, A Coruña, Spain, 2Department of Cardiology, Complexo Hospitalario Universitario de A Coruna (CHUAC)-INIBIC, A Coruña, Spain, 3Department of Cardiology, Complexo Hospitalario Universitario de A Coruña (CHUAC)-CIBERCV, Instituto de Investigación Biomédica de A Coruña (INIBIC), Universidad de A Coruña (UDC), A Coruña, Spain. P05.032.B The expression level of cytokine genes in the cases of native heart valves in infectious endocarditisMaxim Sinitsky, Anna Tsepokina, Maria Khutornaya, Anastasia Ponasenko Research Institute for Complex Issues of Cardiovascular Diseases, Kemerovo, Russian Federation. Kuentz: None. Vanlerberghe: None. Results: 603/13612 (4.4%) patients were identified of whom 453/603 (75.1%) had trio ES. Methods: Carriers of double PVs in any DNA MMR gene and BRCA1/2 attending one of three tertiary oncogenetic clinics between 1/2005 and 1/2020 were identified by database search, and their relevant data were retrieved and analyzed. Likely pathogenic rCNVs of 4 patients, located on 3 chromosomes, contained one of miR-548 members. Differentially methylated regions (DMRs) (>5.0-fold change) between HSCR and controls, were identified and used for a supervised hierarchical cluster analysis. Type V OI, caused by recurrent dominant mutation in IFITM5/BRIL, and type VI OI, caused by recessive null mutations in SERPINF1/PEDF, have distinct features. Andriamboavonjy: None. Zenker: D. Suri: None. Methodology: A total of 49 unrelated patients with clinical features of ADPKD were studied using a customized gene panel for genes associated with polycystic kidney disease (PKD) using next generation sequencing (NGS). Ellard: None. However, this will likely improve soon, with highly powered GWAS summary statistics that will likely become available for more commonly measured traits. Aiming to test the effect of the AGG interspersions, our group developed a mathematical model that combines the AGG interspersion number and pattern as well as the FMR1 total repeat length. In addition, we found higher frequencies of CLMs, ULMs and RCys, than those with loss-of-function variants (p T missense variants. Lindenberg: None. Medical geneticists usually try to identify patients' clinical conditions by recognizing the specific pattern of a syndrome. Funding: MOBTP175, PRG471 S. Validation genotyping of filtered rare silent and missense variants revealed that the majority of them were true variants. Lapina: None. Bednářová: None. Hattersley1, Michael N. At the end, we asked participants to find solutions: imaginary ideal ones and real, possible to implement here and now. Results: From a total of 2380 patients included in the database we identified 24 patients (1,0%) with chromosome 1 CNVs, P (9 cases) or VOUS-PP (15 cases). Materials and Methods: Non-pregnant women visiting their gynaecologist were invited to complete a questionnaire assessing socio-demographic characteristics, the perceived susceptibility of being a carrier/conceiving a child with a hereditary condition, the acceptability of offering ECS, attitudes towards ECS, the intention to participate in ECS and reasons to accept or decline ECS. We used UK biobank (UKBB) GWAS summary statistics for corresponding phenotypes and selected optimal p-value thresholds for maximizing R2 for PRS. Estivill: None. Whole exome sequencing (WES) is an important diagnostic tool for individuals affected by neurodevelopmental disorders (NDD) and/or multiple congenital anomalies (MCA). In 25 % of cases, we have identified a pathogenic or likely pathogenic variant (as per the ACMG guidelines) likely causative of the fetal phenotype. We should therefore be careful to assign observations in present-day data to specific historical events. This diagnosis was finally confirmed, in another case of NIHF, by the absence of beta-D-glucuronidase activity in the amniotic fluid. We investigated individuals' motives for participating in such projects and potential reasons for their withdrawal from participation in a population-based biobank. Herein, we describe clinical and molecular findings of a female patient analyzed by clinical exome sequencing (CES). Here we investigated this phenomenon by studying the distribution of alleles and the effect of consanguinity in different groups of disorders. Monoallelic (likely) pathogenic variants in COL4A3/4 in an AS case were not considered as diagnostic, as the designation "autosomal dominant AS" is contested. Supported by the Italian Ministry of Health (GR-2013-02357561). Lara Cantón: None. Introduction: Acute appendicitis is one of the most common abdominal emergencies worldwide. Employment (full or part-time); Significant; Miroculus, Inc. A proper follow up of every abnormal result should be considered. EDC4 and RECQL5 genes were included from collaborators' publications. Conclusions: All these data underscore the significant proportion of URD diagnosed in CM/ID and the limited information available to patients and their families on their evolution and management. Eight patients had different variants in GNE gene. The aim of research is to study the polymorphisms of genes of energy metabolism (LEPR; FTO) and angiogenesis (NOS3; VEGFA) in women with IUGR compared to the control group to identify it`s possible functional significance in the pathogenesis of IUGR. Gumilyov Eurasian National University, Nur-Sultan, Kazakhstan, 4Medical University Astana, Nur-Sultan, Kazakhstan. Testing for EGFR/ALK status and PD-L1 expression will help for guidance of treatment strategy. Maas6, H E. Copy number variants (CNV) are increasingly recognised as an important aetiology of many human neurodevelopmental disorders, including epilepsy. N.J. Hernández: None. Arold: None. P14.015.D Incidental finding of DFNB1 locus deletion carriers associated with non-syndromic deafness after prenatal analysis in amniotic fluid Matías Pérez, María Luz Bellido, Teresa de Haro Hospital Universitario Virgen de las Nieves, Granada, Spain. Blood phenylalanine levels in our patient ranged from 896 to 2257 µmol/L since diagnosis at the age of 30 (except during her second pregnancy). Aldinger2, David B. In this study we found three variants previously described in patients with hypercholesterolemia. Physicians and laboratories can choose to analyse all of the genes on the panel or focus on a specific genes or subpanels only. Conclusions: Our results provide the first estimates of minimum prevalence of CPEO, revealing single mtDNA deletion and the mtDNA elicase (TWNK) as major genetic cause.Supported by "Programma di ricercar Regione-Università 2010-2012" (PRUa1RI-2012-008) L. Aiza: None. Nayak, Shravya MS, Katta M. Russo: None. Patients with the CDC20-rs710251 CC had shorter overall survival (53.7 months) in comparison to patients with AC or AA genotypes (131.7 and 133.5 months). Kurian: None. Bento: None. Foster: None. Y.J. Bignon: None. Results: Haplogroup H in probands resulted protective for ASD, counterbalanced by increased risk conferred by haplogroups L and I. Molecularly characterized by a ring or a giant marker / rod chromosomes composed of material from 12q13-15. Isokallio: A. Familial hypercholesterolemia (FH) is the most common genetic disorder conferring an increased cardiovascular risk due to cholesterol accumulation since birth. However, breakpoints mapping and eventual deletion of the distal part of chromosome 16q were not possible. Introduction: Variants in spermatogenesis-associated protein 5 gene (SPATA5) are associated with "Epilepsy, Hearing Loss and Mental Retardation Syndrome". P23.022.B Lessons learned from incidental findings in clinical exome sequencing of 16,482 individuals Vyne van der Schoot 1, Lonneke Haer-Wigman2, Ilse Feenstra2, Femke Tammer2, Anke J. Furthermore, we develop a framework needed for FAIR and ethical implementation. Antoñanzas-Perez: None. Madden24, Jennifer E. The symptoms of the proband correspond to the severe autosomal recessive Segawa syndrome with dystonia onset in the early neonatal period. Chludzinska: None. The FBN1 gene was originally screened by bidirectional Sanger sequencing and later by NGS custom capture array. In 3/117 and 8/94 patients a (likely) pathogenic variant was demonstrated. This allows their genetic characterization, even when no clinical and familiar data are available, leading to their reclassification. Third-party interpretation platforms further challenge stakeholders. Introduction: Although next-generation sequencing (NGS) has drastically improved diagnosis for patients with rare diseases (RDs), access to knowledge of effective treatments is still sparse and often unclear. Finally, we detected the novel recurrent fusion gene NRIP1-MIR99AHG resulting from inv(21)(q11.2;q21.1) in nine patients (1.1%) and LTN1-MX1 resulting from inv(21)(q21.3;q22.3) in two patients (0.25%). Abd A.2, Tatiana Pavlovna Shkurat1, Galina Vladimirovna Karantysh3, V N. Gawlinski: None. Kunstmann: None. Results: KIR-HLAC genotyping was performed in 43 married couples with unexplained reproductive losses. We evaluated long-term uptake, timing and effectiveness of risk reducing mastectomy (RRM) and bilateral salpingo-oophorectomy (RRSO) in healthy BRCA1/2 carriers. M.C. Pittalis: None. Introduction: Progress in genetics and molecular research enabled discovery of mutations in BRCA1 and BRCA2, leading to the development of hereditary breast (BC) and ovarian (OC) cancer. Course, Arvis Sulovari, Kathryn Gudsnuk, Evan E. Itier: None. The present findings document that CEP85L mutations are not necessarily associated with severe phenotypes and relevant MRI alterations, documenting the importance of including CEP85L among the genes involved in the pathogenesis of lissencephaly. Litwin: None. Functional validation is under investigation. Corchete: None. Ellingford1,2, Emma R. Evaluation of patients auditory development was performed with the LittlEARS questionnaire (LEAQ) in three subsequent intervals - at the time of cochlear implant activation as well as in 5th and 9th month after CI. Introduction: The Chylomicronemia Syndrome (QS) is characterized by severe hypertriglyceridemia (>1000 mg/dL or >11.3 mmol/L), abdominal pain, recurrent acute pancreatitis, eruptive xanthomas, and lipemia retinalis. Conclusion: By defining seven novel mutations, this study enriched to the molecular spectrum of VWD type 3, while also providing a further insight for genetic counselling. GWAS results highlighted the involvement of common or low-frequency variants in PP1 and PATJ; however, the role of rare variants in stroke recovery remains unsolved. Introduction: Neurofibromatosis of types 1 and 2 (NF1, NF2) and schwannomatosis form part of rare tumor-suppressor syndromes called neurofibromatosis. Franke1 1Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, 2Department of Genetics, University Medical Center Utrecht, Utrecht, Netherlands. Mühleisen 1,2,3, Ling Zhao1, Dominique Hilger1, Bettina Burger3, Andreas Forstner1,4, Stefan Herms3,4, Per Hoffmann4,3, Karl Zilles1, Katrin Amunts1,2, Sven Cichon1,3,5, Nicola Palomero-Gallagher1,2,6 1INM-1, Jülich, Germany, 2Cécile and Oskar Vogt Institute for Brain Research, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany, 3Department of Biomedicine, University Hospital Basel and University of Basel, Basel, Switzerland, 4Research Platform Genomics, Institute of Human Genetics, University Hospital of Bonn, Bonn, Germany, 5Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland, 6Department of Psychiatry, Psychotherapy and Psychosomatics, RWTH Aachen University, Aachen, Germany. Weinhaeusel: None. P19.030.B Biochemical, epigenetic and genetic components of high altitude adaptation in Tibetans Nipa Basak 1,2, Juan Castillo-Fernandez3, Tsering Norboo4, Lomous Kumar1, Mohammed S. Donostia, San Sebastián, Spain, 4Unit of Movement Disorders, Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville, Spain, 5Department of Neurology, Hospital Universitari i Politècnic La Fe, Valencia, Spain, 6Department of Pediatrics, Hospital Universitario Virgen del Rocío, Seville, Spain, 7Department of Pediatrics, Hospital Sant Joan de Déu, Barcelona, Spain, 8Department of Pediatrics, Hospital Infantil Universitario Niño Jesús, Madrid, Spain, 9Department of Pediatrics, Hospital de Santa Maria, Lisbon, Portugal, 10Department of Pediatrics, Hospital Regional, Málaga, Spain, 11Department of Pediatrics, Hospital Universitario de Cruces, Barakaldo, Spain, 12Department of Pediatrics, Hospital Universitari Son Espases, Palma, Spain, 13Department of Pediatrics, Hospital Universitari Vall d'Hebron, Barcelona, Spain, 14Department of Pediatrics, Complejo Hospitalario de Navarra, Pamplona, Spain. Cruz: None. Reduced/absent GALNS enzyme activity causes impaired degradation of chondroitin-6-sulfate and keratan sulfate and their accumulation in tissues. P05.015.A Diagnostic yield of WES-based gene panels in patients with congenital structural heart defects - a multicenter studyMarrit M. 2: LDSC estimates converted to the liability scale using disease prevalence from UK. P05.013.C A novel missense mutation of TNNI3K associated with cardiac conduction disease Ilyas Ahmad 1,2, Stephanie Tennstedt1,2, Shafaq Ramzan3,1, Shahid Mahmood Baig3, Jeanette Erdmann1,2 1Institute for Cardiogenetics, University of Luebeck, Luebeck, Germany, 2DZHK (German Centre for Cardiovascular Research) partner site Hamburg / Kiel / Luebeck, Luebeck, Germany, 3National Institute for Biotechnology and Genetic Engineering (NIBGE), Faisalabad, Pakistan. The genetic architecture underlying psychiatric and neurological disorders is remarkably complex and highly polygenic. Blake Palculict: A. M.O. Radzhabov: None. López Ballesteros: None. Introduction: More than 90% of patients with Parkinson's disease (PD) have various neuropsychological disorders: depression, anxiety and cognitive impairments. Conventional CD4 T lymphocytes play a central role in the protection of the organism against a wide range of endogenous and exogenous dangers. Pavinato: None. Overall, PGVs in four genes conferred a significant increased risk for LBC. Venturin: None. Brother and daughter of proband also carried rs897543876. RNA-seq revealed out-of-frame exon skipping. Dandy-Walker malformation was present in 72% of the 11 images evaluated. Conclusion: This missense variant was reported in three of the patients described by Szot et al. At our center, we provide oncogenetic consultations and molecular genetic testing for hereditary tumor diseases for whole Luxembourg. Laurent-Puig: None. P09.024.A Unravelling the implication of the major vault protein in neuroanatomical phenotypes at the autism associated 16p11.2 locus Binnaz YALCIN 1, Perrine Kretz2, Christel Wagner2, Charlotte Montillot1, Sylvain Hugel3, Ilaria Morella4, Meghna Kannan2, Anna Mikhaleva5, Marie-Christine Fischer2, Maxence Milhau1, Riccardo Brambilla4, Yann Herault2, Alexandre Reymond5, Mohammed Selloum6, Stephan Collins1 1Inserm, Dijon, France, 2IGBMC, Illkirch, France, 3INCI, Strasbourg, France, 4NMHRI, Cardiff, United Kingdom, 5Center for Integrative Genomics, Lausanne, Switzerland, 6MCI, Illkirch, France. of Pathology and Laboratory Medicine, Riyadh, Saudi Arabia, 9Genetika-Centro de Aconselhamento e Laboratório de Genética, Curitiba, Curitiba, Brazil, 10Universidade da Região de Joinville, Programa de Pós-Graduação em Saúde e Meio Ambiente, Santa Catarina, Brazil, 11Prefeitura de Joinville, Núcleo de Assistência Integral ao Paciente Especial, Santa Catarina, Brazil, 12Mashhad University of Medical Sciences, Dept. O´Callaghan Cord: None. P10.012.D In-depth characterization of mutations causing axonal recessive peripheral neuropathy with neuromyotonia (NMAN): the structure gives a HINT Silvia Amor-Barris 1,2, Tamás Lázár3,4, Kristien Peeters1,2, Shoshana Wodak3,4, Albena Jordanova1,2,5 1VIB - Center for Molecular Neurology, Antwerp, Belgium, 2University of Antwerp, Antwerp, Belgium, 3VIB - Center for Structural Biology, Brussels, Belgium, 4Vrije Universiteit Brussel, Brussels, Belgium, 5Medical University-Sofia, Sofia, Bulgaria. Falkenberg: None. Gyenesei: None. Aguti: None. Duat Rodriguez: None. Pires4, Joana B. Slesarenko: None. P11.035.A Clinical relevance of postzygotic mosaicism in Cornelia de Lange SyndromeAna Latorre-Pellicer1, Marta Gil-Salvador 1, Cristina Lucia-Campos1, Rebeca Antoñanzas-Perez1, Laura Trujillano2, Maria Arnedo1, Ilaria Parenti3, Paulino Gómez-Puertas4, Beatriz Puisac1, Frank J. GBA variants represent an important genetic contributor to early onset and/or familiar PD in the Balkan population. All show stereotypic demeanor, three with behavior disorder. The group consisted of intensive care clinicians, geneticists and laboratory staff. The results point at the need to study less obvious genes of marfanoid syndromes to improve their diagnostics, which may have implications for patient prognosis, as well as diagnosis and prevention in family members.The investigation was supported by Nicolaus Copernicus University grant WL174. Results: At the result of DMD MLPA analysis of patient, we determined heterozygous deletion at 14th and 15th exons. False positive rare genetic variants are a significant problem. Tsygankova: None. Materials and Methods: SOX3 expression in human GBM samples, non-tumoral brain tissues and GBM cells was assessed using RT-qPCR. Semenova 1,2,3, Valentina M. Affected individuals had microcephaly, early-onset psychomotor delay, hyperkinetic movement disorder, truncal ataxia, and elevated creatine kinase (300−1200 UI/L). Genetic variations across Olfactory Receptors (OR) genes influence the diversity of odorant sensitivity among individuals. Material and methods: Descriptive retrospective collaborative study of Spanish children with de novo intragenic variants in SETD5 gene. Materials and Methods: Two unrelated patients with autosomal-dominant (ad) and autosomal-recessive (ar) CRD, and one with arCSNB were examined clinically by standard ophthalmological methods. P12.187.C The molecular consequences of the novel speckle-type POZ protein (SPOP) gene mutations at the protein level: A prostate cancer perspective Isil Ezgi Eryilmaz, Berna Aytac Vuruskan, Onur Kaygısız, Gulsah Cecener, Unal Egeli, Hakan Vuruskan Bursa Uludag University, Bursa, Turkey. Conclusion: These studies confirm YWHAE loss-of-function variants as cause of a new rare neurodevelopmental disease associated with brain abnormalities in human and mouse. LAMP1 promotes virus particle maturation by promoting sufficient pH levels in lysosomes; therefore, LAMP1 overexpression increases viral release.This work was supported by the Ministry of Science and Higher Education of the Russian Federation (agreement # 075-15-2019-1665). Saraiva1,6, Isabel M. d'Annunzio" University of Chieti-Pescara, Chieti, Italy, 4Department of Philosophical, Pedagogical and Quantitative Economic Sciences, "G. Alameldin: None. Eroglu: None. P17.022.A Exploring a strategy for the development of AI-based diagnostic tools for rare diseases Paula Romero-Campo 1, Bertha Guijarro-Berdiñas1, María Jesús Sobrido2, Amparo Alonso-Betanzos1 1Research Center on Information and Communication Technologies (CITIC), Universidade da Coruña, A Coruña, Spain, 2Instituto de Investigación Biomédica A Coruña (INIBIC), A Coruña, Spain. P20.053.D Chromatin LINE1 RNAs control the switch from quiescence to activation in human T lymphocytes Federica Marasca 1, Shruti Sinha1, Rebecca Vadalà1, Benedetto Polimeni1, Valeria Ranzani1, Elvezia Paraboschi2, Renata Grifantini1, Giulia Soldà2, Stefano Biffo1, Sergio Abrignani1, Beatrice Bodega1 1INGM, Milan, Italy, 2Humanitas University, Milan, Italy. Conclusions: To our knowledge, this is the first report of a biallelic loss-of-function mutation not implicated in lethal RD. Christiaans: None. P01.072.D Placental tissue co-expression networks across Russians and Yakuts identify key genes and pathways for preeclampsia Ekaterina Trifonova, Anastasia Babovskaya, Aleksei Zarubin, Anton Markov, Vadim Stepanov Research Institute of Medical Genetics, Tomsk National Research Medical Center of the Russian Academy of Sciences, Tomsk, Russian Federation. Vitan: None. P17.058.A Development of fine-map based polygenic risk scores: an analysis of genetic prediction models for height and LDL cholesterol in UK Biobank Carlo Maj 1, Christian Staerk2, Oleg Borisov1, Peter Krawitz1, Andreas Mayr2 1Institute for Genomic Statistics and Bioinformatics (IGSB), Faculty of Medicine, University of Bonn, Germany, Bonn, Germany, Bonn, Germany, 2Department of Medical Biometry, Informatics and Epidemiology, Faculty of Medicine, University of Bonn, Germany, Bonn, Germany. Introduction: Proximal 6q11q14 deletions are exceedingly rare, particularly the enclosed 6q13q14 microdeletions. Vogelsang: None. By investigating the correlation between epigenetic age acceleration (EAA) and externally visible phenotypes we aim to investigate molecular pathways involved in aging processes and disclose promising targets for antiaging therapies. Perola: None. Material and Method: Whole exome sequencing (WES) coupled with optimized prioritization approaches was used in 10 families with autosomal recessive HA (ARHA). Conclusions: Later ANM is detrimental for hormone sensitive cancers yet benefits metabolic and bone health, consistent with effects of oestrogen therapy in trials. of Genetics, Assistance Publique-Hôpitaux de Paris - Université de Paris, Paris, France, 2Department of Clinical Genetics, Ninewells Hospital and Medical School, Dundee, United Kingdom, 3Manchester Centre for Genomic Medicine, University of Manchester, Manchester, United Kingdom, 4Manchester Centre for Genomic Medicine, Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom, 5UOC Genetica Medica, Fondazione Policlinico Universitario A. Uitterlinden: None. Vadalà: None. Here, we propose a new model, called "Post-Mendelian", that takes into account both common and rare germline variants applied in a cohort of 1,768 Italian SARS-CoV-2 positive individuals. Del Barco: None. P09.040.A Chromosomal aberrations in paediatric patients with epilepsy, with or without additional neurodevelopmental disorders: a single-centre clinical investigation Marlena Młynek 1, Katarzyna Urbańska1, Katarzyna Pachota1, Petr Berko1, Danuta Sielska-Rotblum1, Dorota Wicher1, Agata Cieślikowska1, Agnieszka Madej-Pilarczyk1, Piotr Iwanowski1, Maria Jędrzejowska1,2, Justyna Pietrasik1, Katarzyna Iwanicka-Pronicka1,3, Anna Gutkowska1, Małgorzata Krajewska-Walasek1, Krystyna Chrzanowska1 1Children's Memorial Health Institute, Department of Medical Genetics, Warsaw, Poland, 2Polish Academy of Sciences, Mossakowski Medical Research Centre, Rare Diseases Research Platform, Warsaw, Poland, 3Children's Memorial Health Institute, Department of Audiology and Phoniatrics, Warsaw, Poland. Relationship between RNA expression and protein level differed between CA and DG for different receptors. Tobias: None. Baselm: None. Methods: We screened germline variants in 100 patients (without known clinical/molecular diagnosis of hereditary cancer syndromes) with lung or digestive NET diagnosed under 45 years. Moro: None. Three Lp(a)-SNP scores capturing effects of up to 2,462 SNP over a 2 MB region around LPA were computed. We validated the top splicing event-cancer associations across six splicing types in CancersplicingQTL and found that the top MR associations showed different splicing-type enrichment patterns across different cancers. Material and methods: Next-generation high-throughput sequencing of microRNAs was done at two time-points in 81 at-risk subjects (of whom 35 transited). Xu: None. Although phenotypic findings are highly variable, immune deficiency, congenital cardiac anomalies, speech delay and palatal anomalies are the most common. Table 2 compares the frequency 6 common disorders at different time intervals. There was a 2.9-fold excess of females [26/35(74%)], similar to the ratio in published cohorts of sporadic cases (P = 0.8514). Discussion: Fetal CFMs diagnosed by sonogram, whether isolated or associated with additional sonographic defects, are associated with abnormal CMA findings. We found that when diagnosed with a borderline-common disease, patients are more likely to experience phenotypic variability, which may complicate data analysis methods focused on single gene defects. P12.016.D Uptake and efficacy of bilateral risk reducing surgery in unaffected female BRCA1 and BRCA2 carriers Ruta Marcinkute 1, Emma Roisin Woodward1, Ashu Gandhi2, Sacha Howell2, Emma J Crosbie3, Julie Wissely2, James Harvey2, Lindsay Highton2, John Murphy2, Cathrine Holland4, Richard Edmondson4, Richard Clayton4, Lester Barr2, Elaine F Harkness5, Anthony Howell6, Fiona Lalloo1, D Gareth Evans1 1Clinical Genetics Service, Manchester Centre for Genomic Medicine, Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom, 2Prevent Breast Cancer Centre, Wythenshawe Hospital Manchester Universities Foundation Trust, Manchester, United Kingdom, 3Division of Cancer Sciences, Faculty of Biology, Medicine and Health, St Mary's Hospital, University of Manchester, Manchester, United Kingdom, 4Department of Obstetrics and Gynaecology, St Mary's Hospital, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom, 5Division of Informatics, Imaging and Data Sciences, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom, 6Manchester Breast Centre, The Christie Hospital, Manchester, United Kingdom. Houghton: None. Christou1, Marios Pantziaris1,2, Kyriaki Michailidou2,6, Eleni Zamba-Papanicolaou1,2 1Neurology Clinics, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus, 2Cyprus School of Molecular Medicine, Nicosia, Cyprus, 3Department of Electron Microscopy and Molecular Pathology, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus, 4Department of Hygiene and Epidemiology, School of Medicine, University of Ioannina, Ioannina, Greece, 5Department of Primary Care and Population Health, University of Nicosia Medical School, Nicosia, Cyprus, 6Biostatistics Unit, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus. Results: The discovery GWAS revealed between 5 and 16 suggestively associated loci (P A, IL-12B +1188A>C were conducted by allele-specific PCR and restriction fragment length polymorphism (RFLP) for the STAT3. Vasilyeva1, Rena A. The hyperfunctional IRAK2 rs708035 A allele was more frequent in RA patients than in controls (69.9 versus 62.2%, respectively, p = 0.015). Introduction: Craniofacial malformations (CFMs) account for approximately 15% of congenital malformations. P03.024.D Polymorphisms of glutathione synthetase gene are associated with susceptibility to type 2 diabetes and hyperglycemia Iuliia Azarova, Elena Klyosova, Ekaterina Shkurat, Alexey Polonikov Kursk State Medical University, Kursk, Russian Federation. 543002001 K.R.M. van der Meij: None. Here we report two independent cases with NFIB disruptions that were identified through low-coverage whole-genome mate-pair sequencing (WG-MPS). Mikhailova2, Alexandr F. Fisher, Baljeet Kaur, Xianne Aguiar, Preetha Aravind, Natashia Cedeno, James Clark, Debbie Damon, Ehsan Ghorani, Foteini Kalofonou, Ravindhi Murphy, Rajat Roy, Naveed Sarwar, Mark R. P05.005.C Somatic mosaicism of human coronary artery cells in atherosclerosis Aleksei Zarubin, Anton Markov, Maria Nazarenko Research Institute of Medical Genetics, Tomsk National Research Medical Center, Tomsk, Russian Federation. The study was supported by grants from the Swedish state under the agreement between the Swedish government and the county councils, the ALF-agreement (ALF-725011) and the Swedish Cancer Society (Grant no. FISH-analysis of cultured amniocytes confirmed the deletion on metaphase cells. Kalofonou: None. Bioinformatic analysis identified 33 miR-625-3p targets that were enriched in eight biological pathways. P12.034.B Subpopulation of cancer stem cells are endowed with distinctive behaviorLetícia A. Frequency differences of previously associated SNPs were defined: between Lithuanians and FIN - 2, IBS - 1, CEU - 0, GBR - 0, TSI - 4, AFR - 8, AMR - 5, EAS - 6, SAS - 6. Angius: None. WGS identified a large inversion of 15Mb encompassing the region Xp:g.[16147177_31662545inv] with breakpoints in DMD intron 54 and in GRPR (a DMD downstream gene, OMIM*305670) intron 1. Villamar: None. Results: Among 90 pregnancies with chromosome abnormalities, 53 (58,89%) were terminated. For GWAS analysis (2), a total of seven genes resulted in being associated with MS (p-value T in the ZFHX4 gene. When parental samples were available, both variants were found de novo for 1/16 patient, and one variant de novo for 9/16 patients. Plutino: None. Snegova, S. We performed in vitro studies for 9 variants and confirmed a role in splicing alteration for 6 of them. She was born small for gestational age, after 39 weeks of gestation with a birth weight of 2340g and birth length of 45cm. The testing method was PCR using a panel including the most common 38 mutations in CFTR gene in the European population and the 5T-7T allele polymorphism. 8% of the human genome is covered with candidate cis-regulatory elements (cCREs). M.A. van Slegtenhorst: None. However, the mechanisms underpinning this association remain unclear. Pathogenic mutations in CREBBP or deletions in the 16p13.3 region including CREBBP are causal for RSTS. P12.193.A Inhibitors of TRAIL-induced apoptotic pathway: a study of relative mRNA expression patterns in breast tumors Eirini Roupou 1, Maria Michelli1, Ilenia Chatziandreou1, N.V. Michalopoulos2, Panayiotis Karathanasis3, Andreas C. Hekel: A. Klopstock: None. Materials and Methods: Three patients with YWHAE de novo heterozygous loss-of-function SNVs and 5 patients (3 unpublished) with deletions (T (p.Lys626Met) in SKI and c.1642A>C (p.Ser548Arg) in SOS1 and thus clinical diagnoses were refined. Abbas: None. Marchetti-Waternaux17, A. Lundbeck A/S, Valby, Denmark, 11Centro de Investigación Biomédica en Red Bioingeniería, Biomateriales y Nanomedicina, Madrid, Spain, 12Catalan Institute of Oncology (ICO)-Bellvitge Biomedical Research Center (IDIBELL), Hospitalet del Llobregat, Spain. Horvath: None. Witsch-Baumgartner: None. I.S. Povarov: None. The genes studied were PKD1, PKD2, GANAB, DNAJB11, PKHD1 and DZIP1L. The G Allele frequency in patients with caries was 70.5% compared with 44.7% in caries-free students; while A allele frequency was 21% caries-free and 13% in students with dental caries. Sanna: None. In addition to VGSCs, other gene families including Transient Receptor Potential and Purinergic Receptor seem to play a role in pain modulation. Buhmann: None. Around 15% of cases have the potential to metastasize and with a high rate of recurrence. Laboratory tests showed excess urinary excretion of cationic amino acids supporting lysinuric protein intolerance. OB from both severe patients have upregulation of pathways related to ubiquitination vs controls. Climent Alcalá8, Elena Mansilla1,2,3, Cristina Schuffelmann7, María Dolores Lledín9, Mario Solís1,2, Teresa López1, Patricia Valcorba1,2,3, Sofía Siccha10, María Irene Valenzuela Palafoll4,11, Fermina López Grondona4, Francisca Nieto Aranda1,11, Eduardo Tizzano4,11, Pablo Lapunzina1,2,3, Fernando Santos-Simarro1,2,3 1Instituto de Genética Médica y Molecular (INGEMM) Hospital Universitario La Paz, Madrid, Spain, 2CIBERER, Centro de Investigación Biomédica en Red de Enfermedades Raras, ISCIII, Madrid, Spain, 3European Reference Network Congenital Malformations & Rare Mental Disability (ERN -ITHACA), Madrid, Spain, 4Departamento de Genética Clínica y Molecular, Campus del Hospital Vall d'Hebron, Barcelona, Spain, 5Grupo de Genética Médica, Instituto de Investigación Vall Hebron (VHIR), Campus del Hospital Vall d'Hebron, Barcelona, Spain, 6European Reference Network Craniofacial Anomalies and ENT disorders (ERN-CRANIO), Barcelona, Spain, 7Servicio de Cuidados Intensivos Pediátricos, Hospital Universitario La Paz, Madrid, Spain, 8Unidad de patología compleja pediátrica, Hospital Universitario La Paz, Madrid, Spain, 9Unidad de hepatología pediátrica, Hospital Universitario La Paz, Madrid, Spain, 10Servicio de pediatría, Hospital Universitario La Paz, Madrid, Spain, 11Grupo de Genética Médica, Instituto de Investigación Vall Hebron (VHIR), Barcelona, Spain. Results: Here we report variations in mtDNA regions 305-310 bp and 16184-16189 bp observed in the present study with our previously published data for Sinhalese ethnicity (N = 63 pairs of patient and controls); used for comparison. Three of the variants were novel. Votypka: None. Results: In an Irish population, ALS might be driven by multiple intermediate-length repeat expansion in likely 8 NDREs genes: ATXN2, DIP2B, FRA11AC1, FRA11A, NUTM2B-AS1, PABN1, TK2-BEAN and ZNF713. There were no false positives nor false negatives in our series and no differences were found in terms of repeatability and reproducibility. Microarray assay of the proband exhibited an approximately 2.6Mb loss at terminal 3p26.3 and a 27.7Mb gain of the long arm of terminal chromosome 13 at q31.1q34. The most common genes in diagnostic reports included FANCA (20.7%) associated with Fanconi anemia and SBDS (14.6%) associated with Shwachman-Diamond syndrome. Rodriguez-Salas: None. The age of beginning and stopping are also different. This

retrospective study evaluates the influence of mtDNA genetics on the prognosis in patients with CCRCC.Twenty-one patients following for CCRCC, including four metastatic, were included after informed consent. We selected CF patients homozygous or compound heterozygous for CFTR mutations. However, sitting-to-standing height ratio was associated with greater odd of CBP in males (Table) but with lower odds in females (Table). Conclusion: These findings point toward the crucial role of the epigenetic mechanisms, such as microRNAs, in regulating the tumor microenvironment complexity including the levels of stemness and EMT phenotype. Some countries recommend risk-reducing for cancer prevention and others recommend an early detection. P11.115.A Diagnostic utility of next-generation sequencing panel tests in the diagnosis of skeletal dysplasiasTiia Kangas-Kontio1, Alicia Scocchia2, Satu Valo 1, Kimberly Gall2, Liisa Pelttari1, Johanna Huusko1, Jonna Tallila1, Inka Saarinen1, Johanna Sistonen1, Juha Koskenvuo1, Tero-Pekka Alastalo2 1Blueprint Genetics, Espoo, Finland, 2Blueprint Genetics Inc, a Quest Diagnostics Company, Seattle, WA, USA. Amr, Nesma Mohamad Elaraby, Ghada Y. No family history of thyroid nodules or schwannomatosis was reported. P13.024.A Multisite de novo mutations after paternal exposure to ionizing radiation Fabian Brand 1, Manuel Holtgrewe2, Leonie Weinhold3, Alexej Knaus1, Matthias Schmid3, Dieter Beule2, Peter Krawitz1 1Institut for genomics statistics and bioinformatics, Bonn, Germany, 2Berlin Institute of Health, Berlin, Germany, 3Institut für Medizinische Biometrie, Informatik und Epidemiologie, Bonn, Germany. Morgan: B. Varvagiannis: None. Marchi: None. The subgroup analysis on comorbidity related to MetS revealed that type 2 diabetes was associated with circadian rhythm genes (OR = 1.07, 95% CI: 1.00-1.14, p = 0.04). Boers4, Cornelius E. Krey: None. The present case-control study investigated the association between a functional polymorphism, IL-17RC*rs708567 (G/A), and idiopathic scoliosis in a Bulgarian population sample. Atik: None. P14.028.A Case report: a reciprocal translocation between chromosomes 4 and 12 at a 14 years old boy Sandra Grigore 1, Doina Guzun1,2, Florin R. Khan, Pakistan, 3NUMS Department of Biological Sciences, Rawalpindi, Pakistan, 4Department of Zoology, Mirpur, Pakistan, 5Ludwig Boltzmann Institute of Osteology, Vienna, Austria. Bielska: None. G.C. Dworschak: None. A part of the explanation may be related to the number of centrioles. Employment (full or part-time); Modest; GeneDx. L.B. Henderson: A. of Neurosciences, Riyadh, Saudi Arabia, 7KFSHRC, Dept. D.M.E.I. Hellebrekers: None. Tran: None. Kokkonen: None. Heverin: None. Ramírez: None. MADD encodes a Rab guanine nucleotide exchange factor (GEF) which activates RAB3 and RAB27A/27B and is thus a crucial regulator of neuromuscular junctions and endocrine secretory granule release. Elnashar: None. Clinical presentation of the PC-deficiency is not specific, frequent mutations are not described for the PC gene, thus, the whole exome (WES) and genome (WGS) sequencing could help to find rare cases of this metabolic disease. Subsequently, variants were reclassified and annotation inconsistencies within and between the APC and ClinVar databases were scrutinised and partly solved. Conclusions: We successfully demonstrated the integration and performance of the complete Roche KAPA HyperCap Workflow v3.0 leveraging KAPA Library Preparation and KAPA Target Enrichment reagents on the AVENIO Edge instrument, enabling the broader adoption of NGS in precision medicine and ultimately improving patient outcomes. Using summary statistics for real data, our method revealed that IVW-MR causal effects of BMI on SBP and of SBP on BMI were both significantly overestimated (by 15% and 10% respectively). Pös: A. P02.004.A Clinical and genetic analysis of new cases provides further characterisation of ALDH1A3-related anophthalmia/microphthalmia Yesim Kesim 1, Fabiola Ceroni1,2, Alejandra Damián3,4, Fiona Blanco-Kelly3,4, Carmen Ayuso3,4, Kathy Williamson5, Véronique Paquis6, Dorine Bax1, Claudine Rieubland7, Chamlal Mostafa8, Marta Cortón3,4, Nicolas Chassaing9,10, Patrick Calvas9,10, Nicola Ragge1,11 1Department of Biological and Medical Sciences, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, United Kingdom, 2Department of Pharmacy and Biotechnology, University of Bologna, Bologna, Italy, 3Department of Genetics & Genomics, Instituto de Investigación Sanitaria-Fundación Jiménez Díaz University Hospital, Universidad Autónoma de Madrid (IIS-FJD, UAM), Madrid, Spain, 4Centre for Biomedical Network Research on Rare Diseases (CIBERER), Madrid, Spain, 5MRC Human Genetics Unit, MRC Institute of Genetics and Molecular Medicine, University of Edinburgh, Western General Hospital, Edinburgh, United Kingdom, 6Department of Medical Genetics, Nice Teaching Hospital, Nice, France, 7Department of Human Genetics, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland, 8Department of Pediatrics, Tangier Hospital, Tangier, Morocco, 9UDEAR, Université de Toulouse, UMR 1056 Institut National de la Santé et de la Recherche Médicale-Université Paul Sabatier, Toulouse, France, 10Department of Medical Genetics, Purpan University Hospital, Toulouse, France, 11Department of Clinical Genetics, West Midlands Regional Clinical Genetics Service and Birmingham Health Partners, Birmingham Women's and Children's Foundation Trust, Birmingham, United Kingdom. Many known polymorphisms were also found in 15 out of 95 positive patients, namely p.Gly26Ser (10 patients), p.Thr25Thr (1), c.337-18G>C (2), c.201-31G>A (1), c.70-7C>T (1). Sala-Vila: None. Hospital de Santa Maria. P22.023.B Kabuki syndrome: case series from one local centre Akane Akane Kondo Kondo 1, Nobuhiko Okamoto2, Aki Hayashi1, Mikio Yamasaki1, Mikio Morine1, Kenji Hinokio1, Kazuhisa Maeda1 1Shikoku Medical Center for Children and Adults, Zentsuji, Japan, 2Osaka Women's and Children's Hospital, Osaka, Japan. P09.013.B 'Genetically predicted telomere length is associated with age- and Alzheimer's Disease-related brain structure alterations.' Blanca Rodríguez-Fernández 1, Natalia Vilor-Tejedor1,2,3, Marina García1, Grégory Operto1,4,5, Eider M. Paracha4, Sophie Bel-Vialar3, Emmanuelle Ranza2,5, Federico A. The serum and urine oligosaccharide analysis showed abnormal patterns. The disease history included congenital severe joint malalignment of elbows, hips, knees and feet, continuous hypermobility, severe kyphoscoliosis, osteoporosis with multiple fractures, congenital diaphragmatic hernia, and mild dysmorphic features. Independent validation of CNVs was done by SNP-array. Schramm: None. P12.157.A Proposal of new candidate genes of predisposition to serous ovarian cancer using whole-exome-sequencing of 16 patients with a familial formMathias Cavaillé1, Maud Privat 1, Lorenzo Menicucci1, Flora Ponelle-Chachuat1, Nicolas Sonnier1, Sandrine Viala1, Mathis Lepage1, Mathilde Gay-Bellile1, Nancy Uhrhammer1, Yannick Bidet2, Yves-Jean Bignon1 1Centre Jean Perrin, Clermont Ferrand, France, 2Université Clermont Auvergne, Clermont Ferrand, France. Genetic and phenotypic data (hearing, taste and smell evaluated through sensory functions assessment) of 1152 individuals have been investigated. Conclusion: Patients with previous inconclusive genetic test results must be reevaluated. Oliva-Teles: None. Materials and methods: 316 Covid-19 patients with positive PCR were classified based on the severity of symptoms and group in two: outpatients (n = 103) and hospitalized patients (n = 213, which included hospitalized in plant, ICU and exitus patients). Multi-level supportive interventions are lacking to ameliorate the burdensome physical, emotional, and financial challenges of AYAs with LFS. The patient phenotype shares features related to both gene defect. Vlasova: None. De Sando: None. P05.039.A CELSR1 mutations in primary lymphedema Murat Alpaslan 1, Sandrine Mestre-Godin2, Isabelle Quere2, Guido Giacalone1,3, Pascal Brouillard1, Miikka Vikkula1 1de Duve Institute, University of Louvain, Brussels, Belgium, 2CHU de Montpellier – Hôpital Saint-Eloi, Montpellier, France, 3Department of Lymphatic Surgery, AZ Sint-Maarten Hospital, Mechelen, Belgium. In vivo imaging in a genetic zebrafish model indicated lysosomal dysregulation throughout the brain, including significant abnormalities in progenitor cells, microglia, and cerebellar function. Dutra-Clarke: None. However, their time-consuming and laborious experimental protocols protract diagnostic times by three to fifteen days. The approach is also extensible to other PCR/CE-based assays. Zanobio: None. Introduction: Nail-Patella Syndrome (NPS, MIM#161200) is an autosomal dominant disorder due to mutation or partial/complete deletion of the LMX1B gene, causing haploinsufficiency. P12.102.B Gene panel tumor testing in ovarian cancer patients significantly increases the yield of clinically actionable germline variants beyond BRCA1/BRCA2 Ana Barbosa 1, Pedro Pinto1, Ana Peixoto1, Joana Guerra1, Carla Pinto1, Catarina Santos1, Manuela Pinheiro1, Carla Escudeiro1, Carla Bartosch1, João Silva1, Manuel R. Conclusion: Our study suggests that the genotype AG in the polymorphism rs11545829 of Keap1 gene could increase the risk of developing autoimmune thyroiditis due to an alteration of the cellular response to oxidative stress. Grant: iStemTheOS, Grant No. MIS 5033630/ELKE5876 from the Hellenic Foundation for Research & Innovation. WDR11 protein expression was studied in patient-derived fibroblasts using western blot (WB) analysis and immunohistochemical (IHC) staining. Genotypes CT (NOS3) and CC (VEGFA) were significantly associated with low risk of developing IUGR. Interestingly, loss of aminoacylation-activity does not cause CMT, suggesting a toxic gain of function mechanism. These deletions were confirmed by a PCR analysis of the genomic DNA using primers designed to amplify across both breakpoints of the mutant allele. Conclusions: The 6-12-month treatment with 4-PBA could effectively restore to a sufficient degree the morphology of GBM in both AS mouse models. For a small number of affected individuals, a causative ANKRD11 variant cannot be detected. Our study provides genetic evidence to improve the current understanding of PP pathogenesis and assesses a genetic tool for personalized risk stratification. Although predominantly sporadic, there are PD patients with autosomal recessive (AR) or dominant inheritance. PIK3CA somatic mutations are frequently involved in various cancer types. P12.052.D Concordant molecular profiles between metachronous colorectal cancers: a colonic or rectal metastasis? In comparison to 35% no-show visits during 2019, no-show visits were reduced to 16% (353). Paracchini: None. Kretowski: None. Results: Missense variants in the GTP-ase domain of GSPT2 were found in both index patients. After phenotypic annotation and trio/quartet WES (completed in 573 families), the TUDP network found a causative mutation in 49% of cases. There was a significantly higher risk of polyp detection in all categories compared to the low-risk group. Such approach may lead to misdiagnosis in some families, as balanced rearrangements (such as insertional translocations), cannot be detected by this technique. A.Y. Dolgov: B. More than 90% of severe deficiency patients are homozygous for PiZ (Glu342Lys) mutation located in exon 5. Sørensen1,2, Tuomas O. P08.086.D Xia-Gibbs syndrome - variable clinical manifestation of three cases from a single genetic department Anna Kutkowska-Kaźmierczak, Paweł Własienko, Maria Boczar, Olga Malinowska, Tomasz Gambin, Małgorzata Kruk, Agata Lipiec, Jerzy Bal, Ewa Obersztyn, Monika Gos Institute of the Mother and Child, Warsaw, Poland. The major findings are briefly outlined. Incident dementia was more common in p.C282Y homozygous men (Hazard Ratio HR = 1·83; 95% CI 1·23 to 2·72, p = 0.003), as was delirium (HR = 1·82, 95% CI 1·21 to 2·72, p = 0·004) compared to those without the mutations. Here, we performed a pairwise comparison of TLs in trophectoderm (TE) and inner cell mass (ICM) of human blastocysts. 92% of reads are on target, and panel uniformity is 97%. The disease is characterized by loss-of-function biallelic mutations in TBCK, which leads to a downregulation of mTORC1 signaling and severe changes in brain morphology. Conclusions: MS-risk MHC loci appear to influence TCR repertoire in MS patients, with the risk alleles reducing the diversity and inducing an expansion of specific clonotypes. P09.055.D Identifying lipid metabolism genes with a potential role in the pathogenesis of Frontotemporal dementia through pool exome sequencing Mihail Ganev 1, Dimitar Serbezov1, Lubomir Balabanski1,2, Radoslava Vazharova2,3, Sena Karachanak-Yankova1,4, Olga Antonova1, Dragomira Nikolova1, Marta Mihaylova1, Rada Staneva1, Viktoria Spasova1, Vera Damyanova1, Desislava Nesheva1, Zora Hammoudeh1, Blaga Rukova1, Savina Hadjidekova1, Shima Mehrabian5, Maria Petrova5, Diana Belezhanska5, Lachezar Traykov5, Draga Toncheva1,2 1Department of Medical Genetics, Medical University of Sofia, Sofia, Bulgaria, 2Gynecology and assisted reproduction hospital "Malinov", Sofia, Bulgaria, 3Department of Biology, Medical genetics and Microbiology, Faculty of Medicine, Sofia University "St. Kliment Ohridski", Sofia, Bulgaria, 4Department of Genetics, Faculty of Biology, Sofia University "St. Kliment Ohridski", Sofia, Bulgaria, 5Depatment of Neurology, UH "Alexandrovska", Medical University of Sofia, Sofia, Bulgaria. Verkerk, Jeroen van Rooij, Jard de Vries, Ans M. P19.054.B Heterozygote selection against ID alleles may shape the landscape of autosomal-recessive pathogenic variants in European populations Hila Fridman 1,2,3, Helger G. Penetrance across genes ranged from 4% to 25% based on hospital data, and 8% to 74% when including primary care. In this report, we describe a case of a young man who suddenly died after a fatal arrythmia and additionally resulted positive for SARS-CoV-2 virus with high titer in myocardium. Even though the general link between autophagy and autoimmune diseases is well studied, CLEC16A's physiological function and its role in human disease is still poorly understood. Results/Conclusion: The group of BRCA1/2-PV samples had significantly higher median scores than BRCA1/2-wildtype samples (LOH-score: 28 vs. Ellingford1, Panagiotis I. Heterozygous GCK variant c.471_473del was detected in two patients from the same family with persistent hyperglycaemia. However, some regions could not be detected and therefore, results should be interpreted carefully. Materials and Methods: We used fibroblasts and cybrids carrying different loads of the m.8344A>G mutation to test two different therapeutic approaches: i) the increase of absolute wild type mtDNA molecules, inducing mitochondrial biogenesis by over-expression of PGC1α protein and by NAD+ donor nicotinic acid treatment; ii) the reduction of mutant mtDNA molecules, stimulating the removal of damaged mitochondria, by chronic rapamycin treatment. DNA was extracted from peripheral blood leukocytes. KMJ was funded by the Lundbeck Foundation (R324-2019-1083) K.M. Johannesen: B. We investigated a Turkish family afflicted with SHFM3. Genotyping performed using Illumina GSA and imputation using the Michigan server and HRC reference panel. Huisman: None. Çepni: None. Bionano Genomics' Saphyr platform extracts megabases long DNA, labels at specific motifs, and linearizes through NanoChannels. P24.011.B Identification of the association between amylase gene copy number variations and pancreatic diseases Assel Arginbekova, John Armour University of Nottingham,Queen's Medical Centre, Nottingham, United Kingdom. Guerry: A. Sequencing Illumina DNA PCR-free libraries demonstrated equivalent insert size, coverage and %excluded total metrics compared to manually-prepared libraries with average insert size of 425bp and average yield of 10nM (300ng-500ng input). c.481G>A; p.(Gly161Arg) mutation was found in 45 of 49 patients and comprised 72.4% of identified alleles, which is probably the highest frequency of this mutation worldwide. Results: In patient 1, a 22q13.32q33 duplication encompassing SHANK3 gene was identified. The Se and Sp of this model was 68% and 65%. Missirian: None. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Modest; Russian Foundation for Basic Research. Kokkinou: None. Out Of the 990 prenatal consultations, 643(65%) used tele-technologies. Women who made the decision to terminate pregnancy in the case of identified fetal CA were older, had more children, among them there were more women with higher education. Smart: None. Rolfs: A. Median age at first sign among patients presenting after birth was 5 years. Pendina, Olga A. Widemann, Andrea M. Gacesa: None. Haasters: None. Funding: ESPE RU Grant 2020; ISCIII, Spanish Ministry of Economy and Competitiveness, co-financed by the European Regional Development Fund (PI20/00950); University Basque Country UPV/EHU (PIF17/29). White matter lesions were the most common pathology. M.K. Schmidt: None. Santamariña: None. Other systemic anomalies reported were short stature (5/7), infantile feeding difficulties (3/7), hearing loss (3/7), cleft lip/ palate (2/7), high arched palate (2/7), developmental dysplasia of the hip (2/7), kyphosis/ scoliosis (2/7), pulmonary artery stenosis (1/7) and multicystic kidney (1/7). Viora-Dupont: None. The patients were studied with detail in their phenotype and with a neurological evaluation. Mekiené: None. Trbojević-Akmačić: A. Results: Even though the PLD may have raised numerous questions with regard to its adaptability with advanced technological devices, its system of no-fault, strict liability of the manufacturers remains effective. 3,111 reported variants were identified in 363 genes. Results: The variant p.Gly183Arg in KCNA5 gene was identified in a 68 years old male. Materials and methods: We identified de novo heterozygous pathogenic mutation in GRIN2B gene - p.Glu839Ter. Introduction: Beckwith-Wiedemann spectrum (BWSp) prevalence is tenfold increased in children conceived through assisted reproductive techniques (ART). Introduction: LSS, encoding for lanosterol synthase, has been associated with congenital cataract, autosomal recessive hypotrichosis simplex resp. Conclusion: We found a significant association for several LOXL1 SNPs, whereas no differences were attributable to CACNA1A rs4926244 SNP. We postulate that the C terminal deletion may have variable effects or that there may be some modifier gene(s) involved. Lachgar: None. Our project analyses these questions within their specific contexts in England, France and Germany. Conclusion: T8M detected in CVS poses a significant risk of fetal involvement, and examination of amniotic fluid (AF) and/or fetal tissue should be offered. Aside from language delay, there were no other statistically significant phenotypic differences between individuals with missense variants as compared to loss-of-function variants. Results: Maternal age and antral follicle count were similar between control and mitochondrial groups, except from anti-Müllerian hormone levels. Bilan: None. Andreson: None. P13.027.D Housekeeping gene and protein expression changes in CCD1079Sk cell line during passages Omer Faruk Duzenli 1,2,3, Emrah Yucesan4, Beyza Goncu1,5 1Bezmialem Vakif University, Experimental Research Center, Istanbul, Turkey, 2Istanbul University, Aziz Sancar Institute of Experimental Medicine, Department of Genetics, Istanbul, Turkey, 3Istanbul University, Graduate School of Health Sciences, Istanbul, Turkey, 4Bezmialem Vakif University, Faculty of Medicine, Department of Medical Biology, Istanbul, Turkey, 5Bezmialem Vakif University, Vocational School of Health Service, Department of Medical Services and Techniques, Istanbul, Turkey. P06.019.D Diagnosis of GM1-Gangliosidosis Type II by WES analysis Laura Tonelli 1, Elena Procopio2, Flavia Tubili2, Mariabeatrice Sanchini1, Alessandra Ferlini1, Alberta Leon3, Stefania Bigoni1 1Medical Genetics Unit, Department of Medical Sciences, University of Ferrara, Ferrara, Italy, 2Metabolic and Muscular Unit, Clinic of Pediatric Neurology, Meyer Children's Hospital, Florence, Italy, 3Research & Innovation SRL, Genetic Laboratory, Padua, Italy. The candidates were identified by the obstetricians, and families were recruited by neonatologists before delivery. A.B. Smit: None. We surveyed a newly-formed special interest group for provincial genetic counselling regulation and estimate that there are 484 individuals in Canada to be regulated as genetic counsellors (n = 484), with 89% found in only 4 of 13 jurisdictions. Other intermediate REs in NIPA1, ATXN1 and ATXN2 are known ALS risk factors. We detected widespread differential expression between low and high-grade osteoarthritis articular cartilage for 9,871 genes, differential transcript expression for 189 genes and differences in transcript usage for 79 genes at 5% FDR in the largest transcriptomic study of osteoarthritis to date. Results include relevant genes outside the previously requested panels, and new relevant information not available during the original analysis. Petrovič: None. Van den Hoek: None. Craniosynostosis appears with a prevalence of 1 in 2500 newborns and represents a premature fusion of one or more cranial sutures. P04.065.B Chondrocyte protein co-expression network analysis reveals a link between ECM mechanosensing and glucose metabolism in osteoarthritis Aspasia Destouni 1, Konstantinos C. Our work illustrates that cryptic splice variants may elude DNA-only sequencing and supports broad first-line use of transcriptome sequencing for children with undiagnosed diseases. Cohorts lacking such data can only use sex, which can reveal only half of the mix-ups. We obtained Vero-based cell lines with a deletion of the cytoplasmic N-tail (CT) and transmembrane (TM) domains of the BST2 gene (Vero-BST2Δ221) and with LAMP1 overexpression (Vero.Lu3 and Vero.Lu5), and we investigated the production of coronaviruses in these cell lines. Although studies evaluating the efficacy and metabolic effects of KD have increased recently, the effects of macronutrient-controlled diets remain controversial. Gass: None. Nagabushan: None. Barner: None. Tkemaladze: None. scMuffin integrates any type of cell- or cluster-associated data, and can be used for single-cell multi-omics analyses (e.g. mutations, gene expression). Syndromic oriented fetopathology after TOP of the male index fetus revealed micrencephaly with pronounced hypoplastic frontal lobes, shortened occipital lobes, missing temporo-parietal lobulation and hypoplastic cerebellum. Funded by grants FPU16/06907, FIS16/00369, H2020-MSC-656359, RYC-2017-21636, RTI2018-101960-A-I00, CIVP16A1828, RD12/0019/0034, PRB2;PT13/0001/0041. Alterations in non-coding ACTG2 segments can be under-recognized causes of mild gastrointestinal symptoms and may explain some instances of inter-familial variability. Folding stability predictions pointed towards monomer instability for variants in the β-sheet and dimer instability for variants at the dimer interface. In the ANXA11, PON1, PON3 and GLT8D1 genes we identified 1-1 relevant variants of uncertain significance (VUS), and in the TIA1 gene 4 variants were detected; all have been identified as ALS-associated genetic variants. P04.005.B Pre and post-natal achondroplasia, retrospective series of 64 consecutives cases with analyze of the diagnostic methods and timing issues Genevieve Baujat, Roxana Borghese, Pascale Sonigo, Joana Bengoa, Caroline Michot, Elodie Millischer-Bellaiche, Sophie Rondeau, Beatrice Childs, Tania Attie-Bitach, Bettina Bessieres, Laurent Salomon, Yves Ville, Jean-Paul Bonnefont, Julie Steffann, Valerie Cormier-Daire Necker Hospital, Paris, France. P09.041.B CSF1R-related adult-onset leukoencephalopathy as an important differential diagnostic factor to consider in early-onset dementias Dóra Csabán 1, Péter Balicza1, Anett Illés2, Barbara Trombitás1, Fruzsina Szabó1, Zoltán Grosz1, Mária Judit Molnár1 1Semmelweis University, Budapest, Hungary, 2PentaCore Laboratory, Budapest, Hungary. Results: Association of AT and AA genotypes of IFN-γ and TLR8 with development of poly-resistant TB (85.7% and 57.1%, respectively); GA and AA genotypes of IL-1β and NOS2 with development of MDR-TB (65.2% and 73.9%, respectively); AA genotype of MARCO with development of mono-resistant TB (100%) were detected. In this study we evaluated the viability, migration and angiogenic potential using different combinations of sorafenib, valproic acid (VPA) and metformina in hepatic cancer model. Employment (full or part-time); Modest; Institute of Molecular Genetics of National Research Centre «Kurchatov Institute». 48 candidate methylation markers were evaluated in 88 cfDNAs (44 CRC, 44 controls). NGS used the TruSightOne Illumina gene panel (4813 genes), supported by our Ministry of Health. Tercanli: None. Klein4, Stefan Kirsch4 1Institute of Functional Genomics, Statistical Bioinformatics, University of Regensburg, Regensburg, Germany, 2Center for Human Genetics, Regensburg, Germany, 3Department of Neurology, Bezirksklinikum Regensburg, University of Regensburg, Regensburg, Germany, 4Division of Personalized Tumor Therapy, Fraunhofer Institute for Toxicology and Experimental Medicine, Regensburg, Germany. Alawbathani: None. Väisänen: None. The functional relevance of the most important hits were explored in an immunohistochemistry (IHC) staining and an in vitro HEK293 overexpression model. The phenotype is still expanding. Pastore: None. Lauber Biason: None. Jusélius Foundation, the Emil Aaltonen Foundation and the Jane and Aatos Erkko Foundation to P.K. E. Saad: None. One patient has previously known homozygous variant in the CYP1B1 gene, NM_000104.3:c.685G>A. van der Laan4, the SiGN consortium 1Center for Molecular Medicine, University Medical Centre Utrecht, Utrecht, Netherlands, 2University of Maryland School of Medicine, Baltimore, MD, USA, 3Oncode Institute, Utrecht, Netherlands, 4Central Diagnostics Laboratory, Division Laboratories, Pharmacy, and Biomedical Genetics, University Medical Centre Utrecht, Utrecht, Netherlands. Interestingly, all YIF1B missense variants encountered localized in, or close to, the transmembrane domains, which were previously shown to be essential for YIF1B function. Zemni: None. Hamzaoui: None. Girisha 1 1Kasturba Medical College, Manipal, Udupi, India, 2Mediscan Diagnostic Centre, Mangalore, Manglore, India. Cuello-Almarales: None. Introduction: The ASCL1-HOX2A-PHOX2B developmental cascade has been proposed as a candidate pathway for Congenital central hypoventilation syndrome (CCHS) and Haddad syndrome (CCHS associated to Hirschprung disease). All these case were confirmed using customized MLPA. In addition, this case-control study revealed statistically significant association between IL-17RC*rs708567 (G/A) and primary scoliosis in males, females, adolescents, familial and sporadic cases. 33%), nilotinib (20% vs. Robertsonian translocation (RT) is one of the most common balanced structural aberrations. Results: In ABCA4-associated Stargardt disease (SD) genotype [p.L541P, p.A1038V] of «frequent» mutations was revealed in 9 patients, in 2 cases in was associated another «frequent» mutation p.G1961E. Conclusions: The results might indicate that for some visitors, dialogue increases the acceptance of HGGE for severe heritable diseases, possibly because participants exchange perspectives with people who experience such diseases. To understand if this event was restricted to a geographical area or whole island, we analysed about 3500 Sardinians, revealing a frequency of about 2% heterozygotes distributed overall in Sardinia. Lorenzo-Salazar: None. We would like to emphasize that physicians should pay attention to immunodeficiency in SOPH patients to start appropriate treatment. Valente: None. Celinćak: None. Introduction: The Undiagnosed Rare Diseases Program, SpainUDP, (is an institutional Program which has the aim of finding a diagnosis for people with unsolved rare diseases. van der Graaf: None. The structure of the data warehouse allows interoperability with the most important international research projects on ageing. Bièche: None. Theodoridou: None. Bashir: None. Materials and Methods: For minigene assays, a genomic segment encompassing the region of interest of PAX6 was cloned into expression vectors and variants were introduced by site-directed mutagenesis. Karaca: None. Results: The methylation markers SEPT9, DCC, BOLL and SFRP2 were present in all patients at baseline and displayed a stronger correlation with tumour volume than CEA and CA 19-9. Corsaro: None. P11.130.D Epileptic encephalopathy as a new feature of TSPYL1 variants, associated with sudden infant death with dysgenesis of the testes Benoit Mazel 1,2,3, Candace Ben Signor4, Véronique Darmency5, Delphine Mallet6, Valentin Bourgeois7, Margot Grisval1, Alexandra Pillard3, Charlotte Poe7, Marie Bournez1, Christel Thauvin-Robinet1,2,7, Antonio Vitobello3,7, Yannis Duffourd3,7, Christophe Philippe3,7, Laurence Faivre1,2,7, Sophie Nambot1,2,7 1Centre de Génétique et Centre de Référence Anomalies du Développement et Syndromes Malformatifs, FHU TRANSLAD - Centre Hospitalier Universitaire Dijon Bourgogne, Dijon, France, 2Fédération Hospitalo-Universitaire Médecine Translationnelle et Anomalies du Développement (FHU TRANSLAD), Centre Hospitalier Universitaire Dijon Bourgogne et Université de Bourgogne-Franche Comté, Dijon, France, 3Laboratoire de Génétique chromosomique et moléculaire, UF Innovation en diagnostic génomique des maladies rares, Centre Hospitalier Universitaire Dijon Bourgogne, Dijon, France, 4Centre de référence du syndrome de Prader-Willi et autres syndromes avec troubles du comportement alimentaire, Centre Hospitalier Universitaire Dijon Bourgogne, Dijon, France, 5Service de Neurophysiologie Clinique, Hôpital d'Enfants, Centre Hospitalier Universitaire Dijon Bourgogne, Dijon, France, 6Service d'hormonologie, endocrinologie moléculaire et maladies rares, CPBE, groupement hospitalier Lyon-Est, Lyon-Bron, France, 7Inserm UMR1231 GAD, Génétique des Anomalies du Développement, Université de Bourgogne, Dijon, France. Whole-genome sequencing data were available for genetic analysis. A characterization rate of 52% was obtained, being 6 cases incompletely characterized with a gene that partially explained the phenotype. The incidence of monozygotic (MZ) twins in BWS patients is higher than in the general population. A total of 74 patients were tested using bone marrow samples and G-banding technique. Ziyyat: None. Introduction: Some multiple primary colorectal cancers (CRCs) (synchronous or metachronous) may derive from a similar clonal origin. IFITM5-S40L mutations causes severe dominant atypical type-VI OI (aVI) with phenotype, bone histology and decreased cellular secretion of PEDF similar to type VI OI. Masny: None. The gene variants were summarized in Table1. Reverse transcription was conducted on each of the pool samples via miScript-II-RT Kit,Qiagen. Materials and Methods: We performed a literature synthesis of genome wide association studies and their meta-analyses that investigated AD susceptibility. P18.003.A Association of bradikinin receptor genes (ins / del (9b)), chimase 1 (1903A> G), and FTO (rs9939609) with obesity in children and adolescence Olga V. Borg Carbott: None.

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