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Abstract book

Session 1: new genes

Associated anomalies in cases with oral clefts (C. Stoll, Strasbourg)

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Cases with oral clefts (OCs) often have other associated congenital anomalies. The reported prevalence and the types of associated anomalies vary between different studies. The purpose of this investigation was to assess the prevalence and the types of associated anomalies in a geographically well defined population. The prevalence and the types of associated anomalies in cases with OCs were collected in all live births, stillbirths and terminations of pregnancy between 1979 and 2007 in 387,067 consecutive births in the area covered by our population-based registry of congenital anomalies. Of the 789 OCs cases ascertained during this period (prevalence of 20.4 per 10,000 births), 39.5% had associated non-OCs anomalies. Associated anomalies were more frequent in cases with cleft palate (52.4%) than in cases with cleft lip and palate (37.3%) and in cases with cleft lip only (16.8%). There were 94 (11.9%) cases with chromosomal abnormalities, including 27 trisomies 13, 15 trisomies 18, 2 trisomies 21, 12 22 q11.2 deletion, 24 other partial autosomal deletions or trisomies, and 14 gonosomal anomalies and 38 (4.8%) cases with non-chromosomal recognizable conditions including syndromes: Meckel, 3 cases, and 2 cases each , Stickler, van der Woude, EEC, CHARGE, Xq fra, and one case each branchiooculofacial, Crouzon, Nager, Treacher-Collins, Cornelia de Lange, Ivemark, multiple pterygium, orofaciodigital, Klippel-Feil, Moebius, otopalatodigital, Larsen, Kniest, Adams-Oliver, Roberts, thanatophoric dysplasia, Robinow, Fryns, Seckel, Silver-Russel; associations: VATER, 2 cases; spectrums: OAVS, 2 cases and sequence: one case of fetal akinesia. Hundred eighty cases (22.8%) were multiple congenital anomalies (MCA). Anomalies in the musculoskeletal system (16.7%), the central nervous system (15.0%), the urogenital system (13.7%), the cardiovascular system (8.6%), and the digestive system (6.6%) were the most common MCA. In cases with associated non-chromosomal anomalies, prenatal detection rate was 25.0% in the cases with cleft palate and 83.9% in the cases with cleft lip/palate. The overall prevalence of associated anomalies, which was four out of ten cases emphasizes the need for a thorough investigation of cases with OCs. A routine screening for other congenital anomalies especially of the musculoskeletal, the central nervous, the urogenital, the cardiovascular, and the gastrointestinal system may need to be considered in infants and in fetuses with OCs.

Cases with oral clefts (OCs) often have other associated congenital anomalies. The reported prevalence and the types of associated anomalies vary between different studies. The purpose of this investigation was to assess the prevalence and the types of associated anomalies in a geographically well defined population. The prevalence and the types of associated anomalies in cases with OCs were collected in all live births, stillbirths and terminations of pregnancy between 1979 and 2007 in 387,067 consecutive births in the area covered by our population-based registry of congenital anomalies. Of the 789 OCs cases ascertained during this period (prevalence of 20.4 per 10,000 births), 39.5% had associated non-OCs anomalies. Associated anomalies were more frequent in cases with cleft palate (52.4%) than in cases with cleft lip and palate (37.3%) and in cases with cleft lip only (16.8%). There were 94 (11.9%) cases with chromosomal abnormalities, including 27 trisomies 13, 15 trisomies 18, 12 22 q11.2 deletion, and 40 other chromosomal abnormalities, 38 (4.8%) cases with non-chromosomal recognizable conditions including syndromes, associations, spectrums and sequence and 180 cases (22.8%) with multiple congenital anomalies (MCA). Anomalies in the musculoskeletal system (16.7%), the central nervous system (15.0%), the urogenital system (13.7%), the cardiovascular system (8.6%), and the digestive system (6.6%) were the most common MCA. The overall prevalence

of associated anomalies emphasizes the need for a thorough investigation of cases with OCs. A routine screening for other congenital anomalies need to be considered in infants and in fetuses with OCs.

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FOSL2 stop mutations in the last exon cause a recognizable phenotype of scalp defect and enamel defects: description of 9 patients (A Cospain, Rennes)

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We report on a new recognizable syndrome including nine individuals with pathogenic heterozygous variants in *FOLS2* gene identified through an international collaboration.
The reported individuals share a striking similar developmental phenotype including intrauterine growth retardation, scalp aplasia with or without skull defects and enamel teeth abnormalities. Some patients also showed neurodevelopmental impairment with a mild psychomotor retardation (4) or intellectual deficiency (2), focal seizures (2), autism spectrum disorder (3). We noticed also 3 patients with congenital cataracts. Dysmorphic facial features are present but non-specific. Two patients presented immune dysfunction, one a specific polysaccharide antibody deficiency needing immunoglobulin replacement therapy and recently lichen sclerosus, the other a deregulate proportion of non-switched/switched memory B cells. The immunological investigations within these other patients are in progress.
Whole exome sequencing identified 6 variants in *FOSL2* which occurred *de novo* in all of them. Two affected sisters were observed, raising suspicion of a germline mosaicism in one of the unaffected parents.
FOSL2 (*FOS* Like 2, AP-1 Transcription Factor Subunit, also called FRA2) is a member of the Fos gene family and part of the AP1 transcription factor complex, interacting with cJUN and other proteins. AP1 transcription factor, represses Treg development and controls autoimmunity. Mice overexpressing Fosl2 indeed show a systemic inflammatory phenotype, with immune infiltrates in multiple organs.
All variants were likely gene-damaging variants (nonsense or frameshift), located in the final exon of the gene. We documented that the mutant mRNAs escape nonsense mediated mRNA decay in three patients, where biallelic expression was found at the mRNA level in short time lymphocyte cultures. In addition, we have shown that two

truncated FRA2 (FOSL2) proteins (R199* and Q207*) are more resistant to degradation by the proteasome than the wild-type, leading to increased stability of cJUN and, likely, the AP1 complex.
These findings indicate a role for *FOSL2* in human pathology, associated with a distinct phenotype including intrauterine growth retardation, scalp aplasia, skin and teeth abnormalities and possibly an immune disorder.

A novel homozygous variant in GJA1 causing a Hallermann-Streiff/OculoDentoDigital Dysplasia overlapping phenotype: a clinical report (A JIMENEZ-ARMIJO, Strasbourg)

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A Moroccan girl presented with a phenotype within the clinical spectrum of both Hallermann-Streiff (HSS, OMIM %234100) and Oculodentodigital Dysplasia (ODDD, OMIM #164200 AD; #257850 AR). She had no learning deficit nor psychomotor regression; however, a language delay was noted. She also had obstructive sleep apnea syndrome and specific craniofacial features pathognomonic of HSS. She suffered from repeated dental abscesses and severe early childhood caries. Clinical and intraoral and panoramic radiographic examination showed enamel and dentin defects, giving a ghost-like tooth appearance. Several clinical features of ODDD overlap those of HSS and may confuse diagnosis, considering that the inheritance of HSS is not fully reported yet. The diagnostic odyssey of this patient ended with the identification by exome sequencing of a novel homozygous alteration in the *GJA1* gene. A missense substitution in exon 2 (Chr6(GRCh37): g.121768554C>G NM_000165.4: c.561C>G p.Cys187Trp) was identified by whole-exome sequencing (WES), suggesting a diagnosis of ODDD. This is the first report of a homozygous mutation affecting the second extracellular loop of the CX43 protein. The alignment of this domain sequence with sequences of other species showed that it was largely conserved between species, with the altered cysteine (Cys187) being highly conserved. This variant was predicted to be deleterious by SIFT and by Polyphen2. It is also not present in healthy people gnomAD database (Exome Aggregation Consortium et al., 2016). Collectively, these findings suggested that this amino acid had an important function. This variant was therefore classified as class 4, likely pathogenic, according to ACMG criteria (Richards et al., 2015).
The molecular basis of HSS remains unsolved, but this new discovered homozygous variant strengthens the hypothesis of an overlapping phenotype/genotype correlation in the intermingled HSS/ODDD spectrum. HSS/ODDD may actually be a single syndrome with clinical features spanning both HSS and ODDD and homozygous variants in specific locations of the *GJA1* gene sequence.

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Pathogenic variants in CDH11 cause Teebi Hypertelorism Syndrome (C Kumps, Ghent)

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Teebi hypertelorism syndrome (THS; OMIM 145420) is a rare craniofacial disorder characterized by hypertelorism, prominent forehead, short nose with broad or depressed nasal root. Some cases of THS have been attributed to SPECC1L variants. Homozygous variants in CDH11 truncating the transmembrane and intracellular domains have been implicated in Elsahy-Waters syndrome (EWS; OMIM 211380) with hypertelorism. We report THS due to CDH11 heterozygous missense variants on 19 subjects from 9 families. All affected residues in the extracellular region of Cadherin-11 (CHD11) are highly conserved across vertebrate species and classical cadherins. Six of the variants that cluster around the EC2-EC3 and EC3-EC4 linker regions are predicted to affect Ca^{2+} binding that is required for cadherin stability. Two of the additional variants [c.164G > C, p.(Trp55Ser) and c.418G > A, p.(Glu140Lys)] are also notable as they are predicted to directly affect trans-homodimer formation. Immunohistochemical study demonstrates that CDH11 is strongly expressed in human facial mesenchyme. Using multiple functional assays, we show that five variants from the EC1, EC2-EC3 linker, and EC3 regions significantly reduced the cell-substrate trans adhesion activity and one variant from EC3-EC4 linker results in changes in cell morphology, focal adhesion, and migration, suggesting a dominant negative effect. Characteristic features in this cohort included depressed nasal root, cardiac and umbilical defects. These features distinguished this phenotype from that seen in SPECC1L-related hypertelorism syndrome and CDH11-related EWS. Our results demonstrate heterozygous variants in CDH11, which decrease cell-cell adhesion and increase cell migratory behavior, cause a form of THS, as termed CDH11-related THS.

SCUBE3 loss-of-function causes a recognizable developmental disorder due to defective bone morphogenetic protein (BMP) signaling (M Niceta, Roma)

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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 proteins (BMP)s, Activin and TGF-β ligands. Pathogenic variants in genes encoding these proteins can dramatically affect development and physiology. 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. Here we report that biallelic inactivating variants in *SCUBE3* have pleiotropic consequences on development and cause a previously unrecognized syndromic disorder. Eighteen affected individuals from nine unrelated families showed a consistent phenotype characterized by growth restriction, skeletal defects, dental anomalies and distinctive craniofacial appearance. In vitro functional validation studies demonstrated a variable impact of disease-causing variants on transcript processing, protein secretion and function, and their dysregulating effect BMP signaling. 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. *Scube3*-/- mice showed craniofacial and dental defects, reduced body size and defective endochondral bone growth due to impaired BMP-mediated chondrogenesis and osteogenesis, recapitulating the human disorder. 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.

The recurrent missense mutation p.(Arg367Trp) in YARS1 causes a distinct neurodevelopmental phenotype (L Averdunl, Düsseldorf)

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Pathogenic variants in aminoacyl-tRNA synthetases (ARS) cause a diverse spectrum of autosomal recessive disorders. Tyrosyl tRNA synthetase (TyrRS) is encoded by YARS1 (cytosolic, OMIM*603623) and is responsible of coupling tyrosine to its specific tRNA. We identified eleven individuals with the recurrent homozygous missense variant c.1099C>T;p.(Arg367Trp) (NM_003680.3) in YARS1. This variant causes a multisystemic disorder with developmental delay, microcephaly, failure to thrive and short statue. Affected individuals have muscular hypotonia, microcytic anemia, hepatomegaly, ataxia, brain anomalies, and hypothyroidism. TyrRS has two additional functional domains (N-Terminal TyrRSMini and C-terminal EMAP-II-like domain) which confer cytokine-like functions. In silico analyses show that the mutation p.(Arg367Trp) does not affect the catalytic domain responsible of enzymatic coupling, but destabilizes the cytokine-like C-terminal domain. Biallelic pathogenic variants that reside in different functional domains of TyrRS cause variable clinical phenotypes [(e.g. p.(Phe269Ser) - retinal anomalies, p.(Pro213Leu)/p.(Gly525Arg) - mild ID, p.(Pro167Thr) - high fatality)].
The diverse clinical spectrum of ARS-associated disorders is related to mutations affecting the various non-canonical domains of ARS, and impaired protein translation is likely not the exclusive disease-causing mechanism of YARS1- and ARS-associated neurodevelopmental disorders.

Genetic bases of Goldenhar syndrome or Oculo-Auriculo-Vertebral Spectrum: update (C Rooryck, Bordeaux)

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The Oculo-Auriculo-Vertebral Spectrum (OAVS) or Goldenhar Syndrome is an abnormality of embryonic development of 1rst and second branchial arches, characterized by hemifacial microsomia associated with auricular, ocular and vertebral malformations. For the past 10 years, thanks to national and international collaborations, we have constituted one of the largest cohorts of OAVS described so far, with nearly 350 patients. However, the clinical and genetic heterogeneity of this spectrum with incomplete penetrance and variable expressivity, make its molecular diagnosis complex. Thus, diverse rare CNVs are associated with OAVS, and we identified the first genes associated with OAVS by exomes and genomes sequencing. *MYT1* is the first and still the most "frequent" OAVS gene, with variants in less than 2% of our patients. We also identified *ZYG11B* gene, encoding a protein associated with ubiquitin ligase E2, having a role in the degradation of substrates by the proteasome. Knock-down experiments of *zyg11* in the zebrafish model show a specific deleterious effect on the development of craniofacial cartilages, as well as a proximal wavy notochord phenotype that may correspond to the vertebral abnormalities observed in the OAVS patients. We also demonstrated abnormal alanine expansion in another gene, *ZIC3*, associated with unilateral microtia and hemifacial microsomia in 8 boys from a large Danish family. This gene is already known to be involved in heterotaxy and congenital heart disease, and plays a role in determining the left-right axis. This biological function could explain the unilateral nature of craniofacial involvement in this family and in the OAVS. We also identified a recurrent missense variant in the *EYA3* gene in two unrelated families. We induced specific craniofacial abnormalities in zebrafish *eya3* morphants, with a phenotype comparable with previous animal models. Proteomic studies on knockdown cell models on *EYA3* through siRNA showed in particular a deregulation of the DNA repair pathway, the oxidative phosphorylation pathway, the protein polyubiquitination pathway and an activation of the retinoic acid pathway. Another approach through experiments of toxic *in utero* exposure of mouse embryos to retinoic acid, at a given stage of development, allowed us to highlight other candidate genes involved in craniofacial malformations, some of which were already known to be associated with OAVS phenocopies. Since 2020, the European Solve-RD project allowed us to perform Whole Genome Sequencing in OAVS patients having a negative exome. Different approaches combining multi-omics and environmental studies are necessary to decipher the etiological bases of this complex disease.

Session 2: syndrome delineation in single cases

Focal facial dermal dysplasia type IV (B.DIMITROV, Brussels)

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We present a 3-month old boy with congenital bilateral preauricular hypopigmented maculae. Born following uneventful ICSI pregnancy. Further clinical assessment detected bilaterally dysplastic ears and no other malformations. There was no family history of similar lesions. Clinically, a diagnosis of focal facial dermal dysplasia type 4 was

suspected. The clinical spectrum of focal facial dermal dysplasia and the underlying molecular pathology will be discussed.

Recessive progressive symmetric erythrokeratoderma due to a compound heterozygous mutation in the *KDSR* gene (V LARA, Reggio Emilia)

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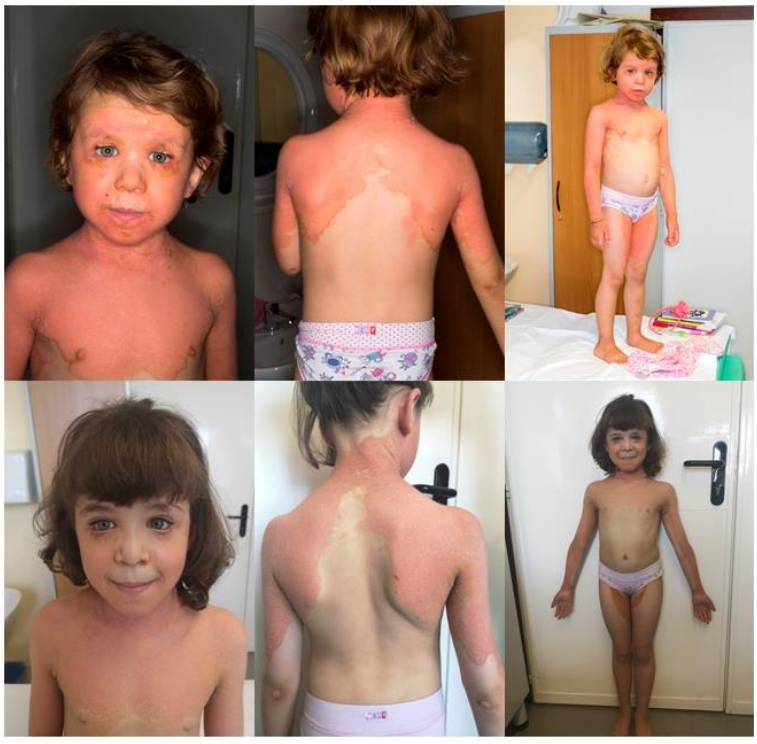
Mendelian disorders of cornification (MEDOCs) are severe skin disorders characterized by localized or generalized scaling and redness, caused by variants in more than 50 genes that share a common pathobiological feature of increased transepidermal water loss. Included among MEDOCs is *erythrokeratodermia variabilis et progressive 4* (EKVP4, OMIM617526), a recently identified recessive condition characterized by neonatal onset of thick, scaly skin on the face and genitals and erythematous palmo-plantar scaling. Previously described Mendelian forms of erythrokeratoderma were usually dominant and often result from heterozygosity for a de novo variant. Conversely, EKVP4 was firstly described in 2017 in four individuals with compound heterozygous variants in the *KDSR* gene. *KDSR* encodes 3-ketodihydrosphingosine reductase, a key enzyme in the novo ceramide synthesis pathway. Ceramides are central to cutaneous barrier function, and current findings demonstrated an important role also in platelet biology. A recent study described four probands with EKVP4 caused by *KDSR* variants accompanied by severe thrombocytopenia and platelet dysfunction in infancy, indicating that biallelic variants in *KDSR* are implicated in an extended spectrum of disorders of keratinization in which thrombocytopenia is also part of the phenotype. Systemic isotretinoin therapy resulted in nearly complete resolution of their scaling and erythema in two patients. To date, EKVP4 represents an extremely rare condition, with only ten cases described. We report an 8-year-old girl, born from an unrelated and healthy couple, with a history of "eczematous skin lesions" on



the face and scalp since 3 months of age, evolving in itchy hyperkeratotic lesions, with inflammation and tendency to the formation of fissures, with widespread localization, but particularly evident on the face, forearms and wrists from 7 months of age. An initial diagnosis of atopic dermatitis was made and, subsequently, Jordan's anomaly was identified at peripheral blood smear and Chanarin Dorfman's syndrome was hypothesized but then excluded due to the negativity of the genetic investigation. A genetic panel for Ichthyosis/Keratoderma/Hyperkeratosis (*KRT1, KRT10, KRT9, KRT2* genes) was inconclusive and molecular analysis of *GJB3-GJB4* genes causing erythrokeratoderma variabilis autosomal dominant showed a negative result. Based on phenotypic similarities with the patients published by Boyden et al. (2017) EKVP4 was suspected. Sanger sequencing of the *KDSR* gene revealed the genomic variant c.[879G>A](p.[(Gln293Gln)] with paternal segregation. The variant was a synonym located in the canonical site of splicing and was present in hemizygosis. A deletion on the corresponding maternal allele was also demonstrated. Therapy with systemic retinoic acid derivative (acitretin before, isotretinoin thereafter) slightly improved the erythrodermic skin lesions, especially on the face and legs (Fig.1). No thrombocytopenia was identified during follow-up.

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First case report of complete paternal isodisomy of chromosome 10 harboring a novel variant in COL17A1 of non-Herlitz junctional epidermolysis bullosa (Yao Wang, Shanghai)

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Background: Uniparental disomy (UPD) is a condition in which both of a chromosome are inherited from the same parent, except for imprinting disorders, isodisomy (iUPD) may result in a homozygous variant contributing to an autosomal recessive disorder in the offspring of a heterozygous carrier. Non-Herlitz junctional epidermolysis bullosa (JEB-nH) is an autosomal recessive inherited disease associated with series of gene variants including COL17A1.

Case Presentation: We report the first case of complete paternal uniparental isodisomy of Chromosome 10 harboring a novel homozygous variant in COL17A1: c.1880(exon23)delG (p.G627Afs*56) leading to the clinical phenotype of JEB-nH in a 4-year-old child. Trio-whole exome sequencing (Trio-WES) and in silico data analysis was used for variants identification, sanger sequencing was performed for variants validation, and pathological examination was done as the gold standard for phenotype confirmation.

Conclusion We recommend the approach of WES to be used as a first-tier test for the diagnosis of epidermolysis bullosa especially for pediatric patients, meanwhile UPD events should be detected and analyzed routinely through WES data in the future.

Keywords: non-Herlitz Junctional Epidermolysis bullosa, COL17A1, paternal uniparental disomy, whole exome sequencing, genetic councelling

TRAF7 syndrome – a case report with a severe presentation of hydrocephalus

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We report a two year-old male patient, first child born to a healthy non-consanguineous parents, at 41 weeks by c-section. A prenatal suspicion of aortic arch coarctation was not confirmed on post-natal assessment. He was born with Apgar score of 8/9/9, OFC on 25th percentile, length and weight on 50th percentile. Postnatal echocardiogram showed narrowing of the aortic isthmus without obstruction signs and patent foramen ovale.

At 5 month-old OFC crossed more than 2 percentiles and he was diagnosed with hydrocephalus due to Chiari Malformation type I. He was submitted to endoscopic third ventriculocisternostomy. At 14 month-old due to severe atlantooccipital stenosis a decompressive craniectomy of the posterior fossa and C1 laminectomy was done. At 25 month-old fundoscopic examination demonstrated papilledema and he was treated with ventriculoperitoneal shunting.

At clinical genetic evaluation at 13 month of age he presented with development delay and craniofacial dysmorphic features. These include a prominent forehead with plagiocephaly, blepharophimosis and upslanting palpebral fissures, short philtrum, low-set, posteriorly rotated and protruding ears. He had short neck with slopping shoulders, narrow chest, bilateral clinodactlily of the 5th finger with inter-phalangeal extension limitation, and bilateral feet anomalies with talipes equinovarus and overlapping toes (2nd above halux, and 3/4/5 clinodactyly). The patient showed a staturoponderal delay with growth and weight on 3rd percentile. Axial skeleton evaluation showed additional dorsal (D8-D12) hemivertebrae causing kyphoscoliotic posture. Genetic analysis included a normal aCGH, and clinical exome identified a *de novo* pathogenic variant at TRAF7 gene [c.1570C>T (p.Arg524Trp)].

Germline pathogenic variants in *TRAF7* gene have recently been identified in patients with developmental delay, cardiac, facial and digital anomalies. Our patient has a clinical similarities with those patients recently reported, supporting the gestalt described and further delineating the phenotype.

Searching for pathogenic variants in newly discovered disease genes: expanding the phenotype of TRAF7 developmental syndrome

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Tumor necrosis factor receptor-associated factor 7 (TRAF7) (MIM*606692) is a signal transducer that links members of the TNF-R superfamily to different signaling pathways. Heterozygous missense variants in *TRAF7* have recently been reported in individuals with a developmental disorder involving cardiac, facial, and digital anomalies with developmental delay (MIM#618164) (1). We report a 6-year-old male patient who was referred to our center at the age of 2 years. At birth, dysmorphic features and neonatal hypotonia were noted. He was diagnosed with congenital Morgagni hernia (surgery was undertaken at 5 months) and mild aortic root dilation. At 2 years, he had short stature, wide nasal root, epicanthus, bilateral blepharophimosis and ptosis (requiring multiple surgeries), anteverted nares, low-set and anteverted ears, pectus carinatum, overlapping toes, and joint hypermobility. He had mild global developmental delay and oropharyngeal dysphagia. Brain MRI showed bilateral periventricular pseudocysts. Metabolic screening was normal. CGH-Array and clinical exome sequencing were performed, but no disease-causing variants were found. Trio-whole exome sequencing (trio-WES) was ordered. At this point, the first large-scale analysis of patients with TRAF7 developmental syndrome was published (1), and diagnostic suspicion was raised by the clinician team. Trio-WES revealed a novel *de novo* missense variant in *TRAF7*, c.1936G>A/p.(Val646Ile), which was classified as likely pathogenic according to ACMG criteria. Congenital diaphragmatic hernia had not been previously described in patients with TRAF7 developmental syndrome. This case exemplifies the current conceptual framework for investigating patients with unknown diseases, involving clinical dysmorphology, WES (or whole genome sequencing), and newly discovered disease genes.

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Session 3: Syndrome delineation single cases

Fetal phenotype of cardio-urogenital syndrome caused by haploinsufficiency of *MYRF*

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The gene MYRF encodes a transcription factor that acts as a myelin regulatory factor highly expressed in the development of diaphragm and heart. Haploinsufficiency of *MYRF* has been identified as cause of the cardio-urogenital syndrome (MIM 618280). The common features of this entity are congenital diaphragmatic hernia, heart disease and genitourinary abnormalities described in a total of 16 patients in the literature.
Congenital diaphragmatic hernia is a severe life threatening condition affecting about 1/3000 newborns. Despite advances in treatment, mortality rate remains high (40%). A better understanding causative factors and genetic causes for congenital diaphragmatic hernia may inform about disease prognosis and treatment.
After having made the molecular prenatal diagnosis of cardio-urogenital syndrome by one fetus in our center, we collaborate with other genetic centers to constitute a French prenatal cohort of such cases.
We describe the detailed phenotype of 2 fetuses with *de novo* loss-of-function heterozygous variant in *MYRF*. We specify the data of ultrasound, radiological, histological and pathological exams.
Next-generation sequencing (NGS) has increased the prenatal diagnostic yield of monogenic diseases. That's why phenotypical description and support data analysis are necessary to perform variants interpretation identified by prenatal exome sequencing. While recurrent clinical features in children cases with *MYRF* loss-of function variants already have been delineated, the fetal phenotype still remain to be defined to allow a prenatal distinctive diagnosis.

Expanding the phenotype related to de novo missense variant in HNRNPH2

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De novo missense variants in HNRNPH2 have been reported in association with Bain type syndromic X-linked intellectual disability (OMIM #300986). The gene encodes the hnRNP H2 protein, a member of the heterogeneous ribonucloprotein family. The protein is critical for pre-mRNA processing and trafficking between the nucleus and the cytoplasm.
To date, 38 patients (31 females and 7 males) have been described presenting with developmental delay/ intellectual disability, hypotonia, feeding difficulties and some facial dysmorphism. Additional neurological phenotype consisted of seizures, developmental regression, microcephaly, cerebellar anomalies and behavioral troubles.
Eleven different missense variants have been reported in HNRNPH2. All but 2 cluster within or adjacent to the nuclear localization sequence (NLS) of HNRPNPH2 and a mutational hotspot was found in the aminoacid 206 affected in 29 out of 38 patients. The exact physiopathologic mechanism related to missense variants is currently unknown.
Through ERN-ITHACA collaborative call, we collected 4 unrelated female patients and 2 more siblings, with HNRNPH2 missense variants. Four different and previously reported variants were identified, all in the NLS, and one of them occurring in a mosaic state. We describe clinical and genetic data of affected patients. We discuss the intrafamilial clinical variability and compare our patients with those previously reported. We confirm the severe neurodevelopmental phenotype in patients and broad the clinical spectrum of the disease for some of them.

We started functional studies with Western Blot (WB) analysis in cultured fibroblasts from 3 unrelated patients showing the presence of the protein in patients as in controls. X chromosome inactivation (XCI) assays were assessed in DNA from blood and cultured fibroblasts in the patients and all patients showed an extremely skewing pattern. To determine whether the wild-type or the mutated allele was preferentially expressed, cDNA sequencing was performed.

Description of six novel patients with GLYT1 encephalopathy and biallelic pathogenic variants of *SLC6A9* GENE: from severe fetal form to long-term survival

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Glycine transporter 1 (GLYT1) encephalopathy (OMIM# 617301) is a rare disease, described for the first time in 2016 in a child presenting with a novel form of non-ketotic hyperglycinemia resulting from biallelic pathogenic variants of the *SLC6A9* gene. To date, only six affected children and three fetuses from 2 families have been reported. One fetus presented with nuchal translucency and hydrops, and the two other from the same family presented with nuchal translucency and arthrogryposis, leading to termination of the pregnancy. The six affected children presented at birth with multiple joint contractures, severe hypotonia, respiratory failure requiring long-term mechanical ventilation and failure to thrive. The patients had transient startle responses, hyperreactivity to noise and stimulations, progressive

limb hypertonia with brisk reflexes, global developmental delay and characteristic facial features. The facial features included dolichocephaly, long face, high forehead, bitemporal narrowing, upslanting palpebral fissures, strabismus and facial hypotonia. The patients displayed high levels of glycine in cerebrospinal fluid and an elevated cerebrospinal fluid to plasma glycine ratio. Half of these patients died between the ages of two days and seven months, and the surviving children had global development delay.
We report six additional patients from four families with biallelic pathogenic variants in the *SLC6A9* gene, and further delineate the phenotypic and genotypic characteristics of GLYT1 encephalopathy. The clinical characteristics of our patients were similar to those previously reported, but these novel cases broaden the phenotypic spectrum. We report two further fetuses with a severe prenatal presentation of arthrogryposis and fetal akinesia. Furthermore, we describe long-term survival with overall improvement in four of the patients (aged 18 months to 11 years old) which was previously unreported.

Clinical and molecular characterization of 4 additional patients with *TBL1XR1* mutation.

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TBL1XR1 is highly conserved in all eukaryotes and plays a role in transcription mediated by nuclear receptors. Constitutional mutations in *TBL1XR1* have been associated with several human developmental diseases. On the one hand, the recurrent p.Tyr446Cys mutation was reported in 8 patients with a diagnosis of Pierpont syndrome characterized by developmental delay, hypotonia, facial dysmorphic features, hearing loss, abnormal fat distribution in the distal limbs and other malformations. In 2018, two additional mutations (p.Cys325Tyr and p.Tyr446His) were also described in two patients with Pierpont syndrome. On the other hand, various mutations (nonsense, frameshift, missense mutations ; gene deletions) were associated with non syndromic neurodevelopmental features : autism spectrum disorder, intellectual disability, speech impairment, sleep disturbance, hyperactivity, schizophrenia and west syndrome.
Here we report 4 additional patients with *TBL1XR1* variants at heterozygous state : a mosaic nonsense mutation (p.(ArgR216*)), a de novo intragenic frameshift duplication (c.606_609dup p.(Ser204HisfsTER10)), a de novo missense mutation (p.(Lys374Arg)), and a missense mutation (p.(Tyr245Cys)) not found in the mother (father not available). This last mutation was already described in a patient with Fitzsimmons syndrome. Our patients present with various degree of intellectual disability, speech delay, behavioural troubles (ASD, hyperactivity, self-mutilation) and dysmorphic features. Both patients with a missense mutation show a severe phenotype, including facial features and fingers anomalies overlapping with Pierpont syndrome clinical characteristics. This supports the hypothesis that variable phenotypes may result from different molecular mechanisms, which may be a dominant negative effect with missense mutations in contrast to haploinsufficiency with gene deletion or truncating mutations.

Session 4: Syndrome delineation single cases

Novel heterozygous missense mutation in the kinesin motor domain of KIF22 causing spondyloepimetaphyseal dysplasia with joint laxity (SEMDJL), leptodactylic type, in a boy and his mother

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Spondyloepimethaphyseal dysplasia with joint laxity (SEMDJL), leptodactylic type (lepto-SEMDJL), is an autosomal dominant skeletal dysplasia characterized by postnatal short stature, midfacial hypoplasia, severe joint laxity resulting in limb misalignment and progressive scoliosis. Distinct radiographic findings include small, irregular epiphyses with delayed ossification, metaphyseal vertical striations of the knees, constricted femur necks, thoracolumbar kyphosis or scoliosis with or without platyspondyly and slender metatarsals/metacarpals and phalanges without brachydactyly.
Four heterozygous missense mutations in two adjacent residues in the motor domain of *KIF22* (kinesin family member 22; OMIM *603213) have been described in patients with lepto-SEMDJL; p.Pro148Leu, p.Pro148Ser, p.Arg149Gln and p.Arg149Leu.
We here report a boy and his mother presenting with the typical clinical and radiographic findings of lepto-SEMDJL.
At 7 years old the boy's height was 97.5 cm (-5.2 SD). Physical examination revealed generalized joint laxity but bilateral reduced elbow extension and severe genua valga, for which he received corrective surgery at age 6. Radiographic imaging showed severely delayed bone age (2y7m at 5y5m), bilateral constricted femur necks, small epiphyses of the femur, tibia and fibula due to delayed ossification, heterogeneous metaphyses with characteristic vertical striations and a dextro-thoracolumbar scoliosis (Cobb angle 24°).
His mother's height was 138 cm at 31 years old. She also showed bilateral reduced elbow extension and wore a corset for a dextro-thoracolumbar scoliosis as a child. Radiography of the hands at 11 years showed dysplasia of the carpal bones with gracile metacarpals and premature closure of the metacarpal growth plates.
Duo whole-exome sequencing identified a novel heterozygous missense mutation in *KIF22*; c.677T>G, p.Leu226Arg, in the boy and his mother.
KIF22 encodes a monomeric kinesin and functions as a mitotic motor during chromosomal segregation. The hitherto reported mutations of residues p.Pro148 and p.Arg149 are located in an α-helix of the KIF22 motor domain. Their pathogenic effect resides on motor dysfunction through hydrogen bond disruption. The p.Leu226 residue affected in our patients is also located in an α-helix of the KIF22 motor domain and forms three hydrogen bonds with nearby residues. It is plausible that the missense mutation in our patients, p.Leu226Arg, leads to a similar disruption of hydrogen bonds, hence causing the lepto-SEMDJL phenotype.

Autoimmune disorder in a patient with Rubinstein-Taybi-like disorder and BCL11B frameshift variant

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We report the 20-year follow up of a girl born at term, to cousin parents, with low-normal growth parameters. A diagnosis of Rubinstein Taybi syndrome (RTS) was considered in infancy, based the general Gestalt: downslanted palpebral fissures, hooked nose with low set columella, griming face, crowded teeth, short stature and microcephaly (about – 4 SD) despite normal thumbs. She Raynaud disease in the lower limbs and had retraction of the calf muscles with equine feet that required casts and surgery. She had mild to moderate ID with severe hyperactivity and temper tantrums in infancy. She developed an IPEX like Immune dysregulation syndrome : Basedow thyroiditis was diagnosed at age 5 and coeliac disease in her teens and in her twenties, Biermer anemia. CMA was normal. Reevaluation of a duo exome performed in 2016 recently showed a frameshift variant in *BCL11B*.
BCL11B encodes B-cell lymphoma/leukemia 11B, a zinc finger transcription factor that participates e.a. in the differentiation and migration of neurons and the regulation of the T cell lineage, where it is critical for initial pro-T commitment. It shows dual action (repression/activation) and couples epigenetic regulation to gene transcription, through its interaction with the SWI/SNF (BAF) chromatin remodelling complex, where it cooperates with CREBBP and EP300. *BCL11B* locus is involved in T-cell LAL oncogenesis. LoF variants have been reported in less than 20 patients with a variable phenotype associating craniofacial dysmorphism, ID and deficient immunity. Our patient further expands the phenotypic spectrum of *BCL11B* syndrome to complex dysimmunity syndrome, and emphasizes the clinical overlap with RTS.

Novel *PIEZO2* mutation in a new born with congenital arthrogryposis multiplex

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Background: A female baby patient, first child of non-consanguineous couple of North-European origin was referred to the Genetics Clinic. During the second and third pregnancy trimester, foetal ultrasound assessment failed to detect any congenital abnormalities. The girl was born at 36 weeks of gestation by caesarean section with birth weight of

2230 grams and head circumference of 34.5 centimetres. She was hospitalized in the neonatal intensive care unit for respiratory support. Clinical assessment detected generalised arthrogryposis with severe bilateral clubfeet deformity, bilateral hip dislocation, clenched hands, ulnar finger deviation, clinodactyly, camptodactyly, and dysmorphic facial features such as brachycephaly, mild hypertelorism, central cleft palate, whistling face, low set, and posteriorly rotated ears. The initial treatment consisted of physiotherapy and casting. She was discharged from the neonatal intensive care unit after 20-days and follow-up was arranged in a specialized care facility.
Methods: Gene panel testing for neuromuscular disorders was performed on Illumina NGS sequencing system and class 4 (likely pathogenic) or 5 (pathogenic) variants were reported and subsequently confirmed by Sanger sequencing.
Results: A *de novo* heterozygous class 4 variant c.8199_8202delAATA p.(Leu2733Phefs*10) in *PIEZO2* gene was detected.
Discussion: Congenital arthrogryposis is a broad spectrum of genetic and non-genetic conditions with overlapping clinical features. Heterozygous pathogenic variants in *PIEZO2* are known to cause 3 types of arthrogryposis: Gordon syndrome (distal arthrogryposis type 3), Marden-Walker syndrome and Distal arthrogryposis type 5. These clinically and genetically overlapping syndromes are now considered to represent variable expression of the same disorder. Although there is no clear genotype- phenotype correlation, there are some differences among these syndromes. The clinical features of the presented patient tend most to correlate with Gordon syndrome phenotype, which is typically characterized by clenching of hands and feet, camptodactyly, clubfoot, and less frequently, cleft palate. The detected *PIEZO2* variant is a frame shift variant, resulting in a premature stop codon. It is located 20 amino acids before the normal stop codon and has not been previously reported. This *PIEZO2* gene variant was presumed to be likely pathogenic given that there is another reported patient with proven pathogenic *PIEZO2* gene variant that is located downstream of this PIEZO2 position.
Conclusion: A patient with phenotype of Gordon syndrome is presented, one of the three disorders known to be caused by *PIEZO2* pathogenic variants.

NIHF – PIEZO1 mutations underdiagnosed?

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Hydrops foetalis is the accumulation of liquid in the extravascular compartment leading to soft tissue oedema and/or build-up of liquid in body cavities (pleural effusion, ascites, pericardial effusion). Hydrops foetalis can be divided in immune and non-immune causes with the latter being more frequent. In non-immune hydrops foetalis (NIHF) the main causes are cardiovascular, chromosomal, thoracic, twin-to-twin transfusion and anemia. Idiopathic NIHF has a worst prognosis.
We report the case of a newborn where the pregnancy was marked by the appearance of bilateral pleural effusion and facial oedema in the third trimester.
At birth (at 34 weeks of gestational age) he presented with a chylothorax and oedema of the extremities. There were no dysmorphic traits, and the clinical exam was unremarkable.
The family history was unremarkable.
The caryotype and RASopathie panel that was performed on the amniotic liquid came back normal. The rapid whole genome sequencing highlighted 3 variants in the PIEZO1 mutation (c.64+1G>A class 5, c.3890T>C class 3 and c.6800C>T class 3) which allowed us to pose the diagnosis of autosomal recessive congenital lymphatic dysplasia. The c.64+1G>A is a de novo variant, the c.3890T>C variant is inherited from the father and the c.6800C>T variant is inherited from the

mother. Complementary analysis are on-going to confirm the pathogenicity of the variant from the father, and that the maternal variant is a variant of the norm.

Perinatal lethal course of Alkuraya-Kucinskas syndrome in a newborn with arthrogryposis, multiple pterygia and brain abnormalities

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In recent years, exome sequencing has led to the identification of novel perinatal lethal disorders. One of them is Alkuraya-Kucinskas syndrome (ALKKUCS, MIM #617822), an autosomal recessive multi-system disorder characterized by brain abnormalities, arthrogryposis, and variable organ malformations including heart and eyes.
The underlying cause are loss of function or missense variants in *KIAA1109*, which has been shown to be involved in endosomal trafficking and endosome recycling, but whose function still is not well understood. Up to now, a total of 15 families with ALKKUCS have been described in the literature, 12 of them with a perinatal lethal course and three with a less severe phenotype and longer survival.
We describe a further perinatal lethal case of ALKKUCS in a consanguineous family. Pregnancy was complicated by polyhydramnios, which led to preterm birth in the 31st week of gestation. The baby boy had brain anomalies, severe arthrogryposis with flexion contractures and pterygia, short and webbed neck, a heart defect and facial dysmorphism and died immediately after delivery.
Based on clinical findings we searched for candidate genes in autozygosity regions (SNP-array) and ALKKUCS was suspected. Sequence analysis revealed a rare homozygous missense variant in *KIAA1109* [NM_015312.3] c.6962G>A, p.(Ser2321Asn). This variant has not been described in patients with ALKKUCS before. It affects a moderately conserved amino acid and is predicted to be pathogenic by several in silico prediction tools.
This case underlines the importance of thorough phenotyping in foetuses / neonates with perinatal death and confirms *KIAA1109* as a candidate gene for severe congenital arthrogryposis with brain abnormalities and neonatal lethality.

Xq22.1 microdeletion in a girl with developmental delay and epilepsy: towards the definition of a critical region

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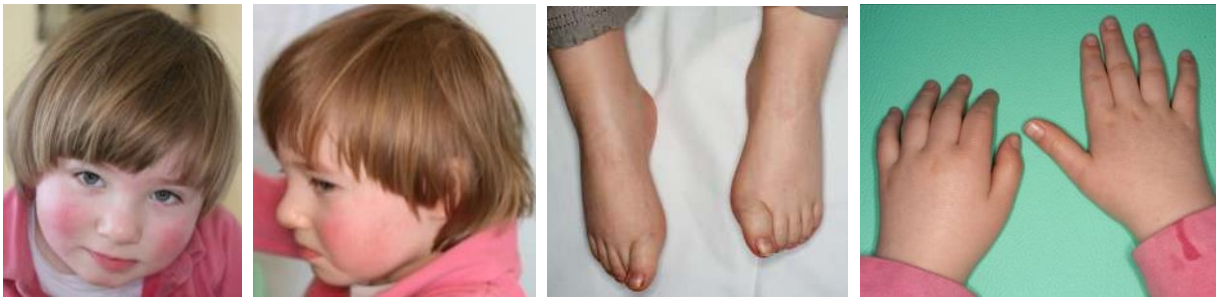
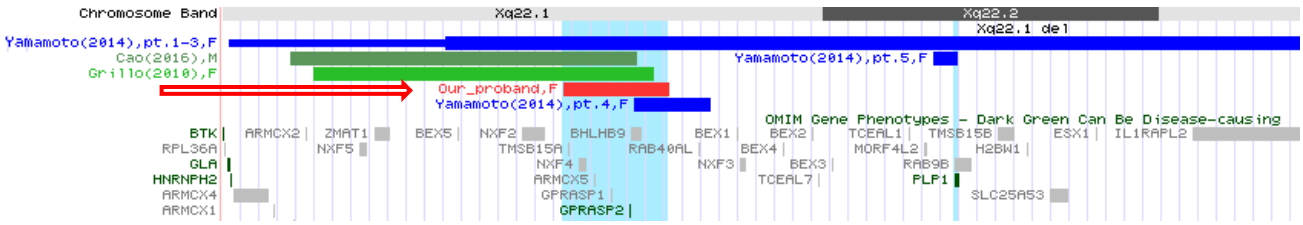
Deletions in the chromosomal region Xq22 have been associated with intellectual disability (ID), epilepsy and various developmental defects in heterozygous female patients, while they are often lethal in males. Recent reports mainly focus on the region encompassing the *PLP1* gene, encoding the major 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).
Here we describe a novel female patient presenting with developmental delay, ID, epilepsy, mild mid-face hypoplasia, small hands, talipes equinovalgus. CGH-array analysis showed a *de novo* 350 Kb deletion in the Xq22.1 region, encompassing the genes *TMSB15A*, *NFX4*, *ARMCX5*, *GPRASP1*, *GPRASP2* and *BHLHB9*. X-inactivation assay revealed a random X-inactivation pattern. Several 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). The 350 Kb deletion in our patient could therefore represent a critical region within the Xq22.1 locus. 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 comprising *Armcx5*, *Gprasp1*, *Gprasp2* and *Bhlhb9*.
Our report supports the notion of a Xq22.1 microdeletion syndrome not comprising *PLP1* but still associated with severe intellectual disability, and sheds some light on its genotype-phenotype correlations.





Session 5: Short reports

A boy with phenotype similar to Cornelia de Lange syndrome – unsolved case (M Vlckova)

Vlckova M. et al.

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During the workshop focusing on presentation of unsolved cases of probably complex syndromic cases, we would like to present a 2,5 years old boy with multiple anomalies and facial dysmorphism, in whom molecular analyses including exome sequencing did not reveal any pathogenic variant explaining his phenotype.
The child was born to non-consanguineous healthy Caucasian parents with unremarkable family history. During the pregnancy IUGR and oligohydramnios occur at the end of the 3rd trimester. He was born via cesarean section because of pathological doppler, his weight was 2490 g, length 49 cm, Apgar score 7 – 9 – 10.
After the birth, dysmorphic features and minor anomalies have been recognized – microcephaly, hypospadias, single palmar crease, small mandible, absence of otoacoustic emissions. The milestones have been delayed. At the age of 21 months, he was able to walk only with support and use no words.
Performed examination (karyotype, arrayCGH, screening of inborn errors of metabolism including CDG, massive parallel sequencing of gene panel „rare diseases" focused on CdLs´genes, WES Agilent Sure Select XT_V6 including analysis using HPO-prioritisation) did not reveal any pathogenic variant explaining the phenotype (only variants inherited from healthy parent or carriership of 1 AR variant).
We still consider CdLS, but we would appreciate any opinion which cloud lead to the final diagnosis.

An inconclusive case of syndromic intellectual disability with tetralogy of Fallot and dysmorphisms

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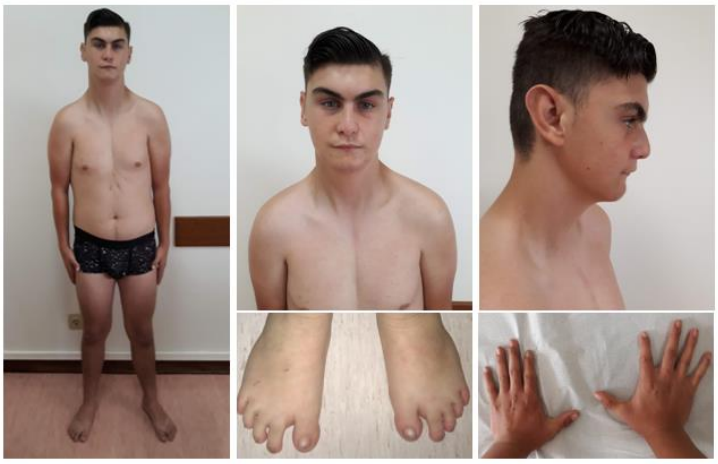
Case presentation: We describe a 15-year-old boy with tetralogy of Fallot associated with multiple dysmorphic features and moderate intellectual disability. He is the second child of first degree cousins of Romani ethnicity. The couple had a third pregnancy with fetal demise of unknown cause at 20 weeks of gestation.
Dysmorphologic examination: The patient is mildly disproportionate due to distal limb muscular hypoplasia. His shoulders are slumped and anteriorly rotated. He presents a syndromic gestalt with highly arched full eyebrows, synophrys, hypotelorism, underdeveloped nasal alae, mild premaxilla prominence, thin lips, and long ears with underfolded superior helix. The distal phalanxes of the hands are hypoplastic with decreased distal interphalangeal creases and reduced articular motility. The feet have short halluces, sandal gap and small nails. The growth parameters are normal.
Investigations: The patient has been followed in Genetics from the age of 7. Fragile X molecular analysis, arrayCGH (CGX-HD 180K, PerkinElmer), and WES-solo with CNV analysis (Centogene AG) were performed, all with negative results.

Discussion and conclusion: We present a syndromic patient with inconclusive etiological investigation. He probably has an undiagnosed autosomal recessive condition, related to parental consanguinity.



An unknown case of a male with intellectual disability and dysmorphic features.

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Here I present an unknown case of a 33 years old male. He has profound intellectual disability, behavior issues, congenital hearing loss, myopia, recurrent ear infections, short stature and scoliosis. He has dysmorphic features, including hypoplastic midface, large protruding chin, deep set eyes, prominent supraorbital ridges, broad neck, and dysplastic ears. In addition, he shows progressive stiffness of the fingers and feet, pyramidal signs and genu valgus.
Genetic testing, including SNP array, whole exome sequencing (trio-analysis), metabolic screening and *FMR1* gene testing showed no clear cause. We did identify a maternally inherited variant of unknown significance in the X-linked *PPP1R3F*-gene.
Suggestions of a clinical or genetic diagnosis are welcome.

Clinical case- trying to find a diagnosis

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We describe an 8-month-baby boy, who is the second son of healthy, non-consanguineous parents, with an uneventful pregnancy. He was born at 31 weeks, needing invasive ventilation due to respiratory failure, hypotension, and severe metabolic acidosis. He presented bilateral microphthalmia with sclerocornea, atrial septal defect, cardiac ventricular disproportion, inferior sinus venosus defect, pulmonary artery branches asymmetry and dysmorphisms (Figure 1).
From family history we stand out a previous medical termination of pregnancy at 23 weeks, due to a polymalformative syndrome in a male fetus (cardiac axis deviation with pericardial effusion, anechogenic abdominopelvic cyst, intestinal duplication, sacral spine hyperlordosis, left microphthalmia, and diaphragmatic hernia). Fetal MRI also confirmed duodenal atresia. ArrayCGH (*Comparative Genomic Hybridisation, CGX-HD 180K, Signature Genomics, PerkinElmer)* and solo exome sequencing were negative. Fetal anatomopathological study was not possible to perform.
The set of manifestations described, and the family history are highly suggestive of a monogenic situation with a high recurrence risk, related with an autosomal recessive inheritance like Matthew-Wood syndrome (*STRA6* gene) and Peter-plus syndrome (*B3GLCT* gene) or an X-linked disorder. Taking into account the genetic heterogeneity underlying overlapping polymalformative conditions that include the features described, a quad familial whole exome sequencing was performed, revealing a negative result.
In this context, we thank you for your help and collaboration in achieving a possible clinical diagnosis or any suggestion to additional investigation. We can offer prenatal ultrasound surveillance in future pregnancies, but the identification of a molecular etiology would have impact on the prognosis, treatment of this baby and accurate family genetic counselling and prenatal diagnosis options.

Figure 1 - Our patient at 8 mo.

Old syndromes and new genes

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Over the years, we tried very hard to make clinical diagnoses. Interacting with the colleges at this and other meetings was very helpful in that respect. Some of those diagnoses were reported in literature.
With the increasing possibilities of molecular genetics, clinical diagnoses could be translated in basic genetic diagnoses. Not only for the small cytogenetic abnormalities, but also for the newly recognized genes.
We show two examples of a reported clinical diagnosis in now adult persons. In both cases time and a new effort showed a de novo molecular diagnosis. The diagnoses were Haspeslagh syndrome and a specific type of arthrogryposis. Both families were very pleased with the new insights.
Take home messages:

1. if you don't find any report about a certain clinical syndrome any more, it may well not exist anymore
2. never give up in looking for a molecular diagnosis

Session 6: Tools in syndrome diagnosis

GESTALTMATCHER DB: labeled medical imaging data for deep learning on monogenic phenotypes

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Motivation: Deep convolutional neural networks (DCNNs) can be used to identify genetic disorders based on medical imaging data. The performance of such tools increases with the size and diversity of the training set and thousands of case reports have been published in recent years in the literature. These data are distributed over many sources and not machine-readable.
Results: GestaltMatcher DB is a web framework designed to empower the scientific community to compile and query labeled data for deep learning applications. The minimal requirement consists of a medical image that is tagged by a disease-causing mutation, gene, or an HPO-term. More than 4000 cases with more than 350 different molecular diagnoses have been contributed within two month, making it the largest data set of its kind.
Availability and Implementation: Applications such as Face2Gene or GestaltMatcher are increasingly used by geneticists and pediatricians in the diagnostic workup of patients with facial dysmorphism. The high performance of these tools is achieved by extending DCNNs. The training of such a network complemented by an additional layer, becomes feasible after knowledge transfer with much fewer data. One of the key challenges is that curation usually needs to be done by clinicians and not computer scientists. Therefore we designed GestaltMatcher DB, a web framework that addresses the needs of human syndromologist first and yields data curation as a by-product.
Human and artificial neural networks need to be trained on image data for pattern recognition. For residents in syndromology, there is no simple way to get exposure to e.g. many characteristic portraits of dysmorphic patients at a glance. By now, the most common use case in GestaltMatcher DB is to query the gallery with a gene, disorder, or phenotypic series.
GestaltMatcher DB focuses on medical imaging data of patients with rare monogenic diseases and is currently mainly populated by but not limited to photos of facial portraits. Additional data under curation are X-rays documenting skeletal malformations and photos of the fundus of the eye documenting retinal diseases.
Clinicians are also asked to provide their expert opinion about the distinctiveness of a phenotype. They have to score whether the medical imaging data was supportive (1), important (2), or key (3) in establishing the clinical diagnosis. Computer scientists can then use this information for the interpretation of performance of their AIs.
The framework is in principle also suitable for contributing health data to research as a referenceable micro-contribution. Clinicians that could attest that they obtained informed consent for publication of images, started sharing these data with the scientific community. We would also like to implement a model of dynamic consent that enables patients directly to define to which kind of research they would like to contribute their clinical data.

GestaltMatcher DB is accessible for registered users on https://gestaltmatcher.gene-talk.de/

Objective evaluation of dysmorphism by automated analysis of facial photographs

Gerrye Mubungu[1,2,3], Prince Makay[1,2,3], Nicole Fleischer[4], Alain Verloes[5], Leon Mutesa[6], Mathieu Roelants[7], Prosper Tshilobo Lukusa[1,2,3,8], Koenraad Devriendt[3], Aimé Lumaka[1,2,8,9]

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The evaluation of “dysmorphism” remains challenging. The presence of three or more minor anomalies is often used as clinical criterion. However, this requires expertise in the evaluation of facial features. The fields of dysmorphology and syndromology are rapidly advancing, triggered by developments in testing technologies such as next generation sequencing, as well as well as automated sorting of syndromes. There is a need for tools that offer a more objective and faster recognition of dysmorphism and syndromes. Face2Gene (F2G) is a widely adopted tool for recognition of syndromes from 2D facial photographs. In the present study, we explored how this tool could aid in the recognition of facial dysmorphism and how it could react to factors such as age, sex and ethnic background.
Different cohorts were studied including unselected Congolese newborns, Congolese children with intellectual disability, children with Down syndrome (DS) from DR Congo and Rwanda (African ethnicity), from Belgium (Caucasian) and Guadeloupe (mixed ethnicity), and a cohort of healthy adult Congolese volunteers. We used F2G to extract facial features from facial photographs, calculate dysmorphism scores and study the effect of ethnic origin, age and gender in different cohorts.
We observed that F2G overestimated the incidence of individual minor facial features in the cohort of Congolese newborns. F2G detected facial dysmorphism, defined as the simultaneous presence of three or more minor facial anomalies, with a sensitivity of 37.5% and a specificity between 94-98%. This suggest that F2G performs better in a holistic approach rather than feature based approach in African individuals. In addition, F2G was able to clearly distinguish Congolese children aged above 15 years from those between 10-14 years based on their facial photographs (AUC=0.874). F2G also distinguished Congolese boys versus girls only from the age of 25 years (AUC=0.998). We concluded that age and gender play a significant role in baseline morphology and in dysmorphism after puberty. It was not possible to separate unselected Congolese newborns based on the geographical provinces of parents within DRC. Interestingly, a clear distinction was made between children with DS from different countries. The African (DR Congo and Ruanda) DS patients were very distinct from Caucasian DS patients from Belgium (AUC=1.000 and AUC=1.000) within the same range of age. Moreover, mixed ethnicity DS patients from Guadeloupe were clearly distinct from Belgian patients (AUC=1.000) but closer to Congolese DS patients (AUC=0.741). This suggests that ancestral genetic background influences the phenotypic expression of DS.

Objective evaluation of facial features in Congolese newborns by facial measurements. An exploratory study.

Gerrye Mubungu[1,2,3], Mathieu Roelants[6], Aimé Lumaka[1,2,4,5], Prince Makay[1,2,3] , Dahlie Tshika[1,2,3], Toni Lubala[7], Prosper Tshilobo Lukusa[1,2,3,5], Koenraad Devriendt[3].

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We evaluated the objective assessment of facial dysmorphism in a cohort of 598 Congolese newborns based on facial measurements. The OCD, PFL and mouth width were significantly larger in Congolese newborns compared to Caucasian, while the ICD, nose width and height and philtrum length were significantly smaller. The IPD calculated from ICD and OCD was not significantly different. We next compared, for hypertelorism, clinical judgement with measurements. IPD was higher in newborns with clinical hypertelorism but the figures show a considerable overlap with clinically normal newborns. We then assembled facial pictures of 105 newborns: the 35 cases with clinical hypertelorism, 35 cases with the highest IPD values and 35 random cases. Pictures were scored by 6 experienced clinicians as hyperteloric (score 1) or normal (score 0). The overall interrater agreement was moderate (kappa of 0.432). The 35 cases with clinical hypertelorism had a mean summed score from the 5 raters of 3.2 (+/- 1.6), significantly higher than 1.3 (+/- 1.5) for the 35 cases with the highest measured IPD but no clinical hypertelorism ($p < 0.001$) and 0.86 (+/-1,3) for the 35 random cases ($p < 0.001$). We compared for the 3 groups the percentage of newborns rated as hyperteloric by 0-5 clinicians. Compared to the “high ipd group” and “average ipd group”, newborns with clinical hypertelorism were significantly more often scored as hyperteloric. This indicates that the clinical evaluation of hypertelorism is not merely reflecting the IPD.

Curation of neurodevelopmental disorder entities in the SYSID and SYSNDD Databases

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The broad application of exome sequencing in genetics has greatly advanced gene identification during the last decade. Neurodevelopmental disorders (NDD) are the most common reason for consultation and diagnostics in

genetic centers in Europe. Their immense genetic heterogeneity paired with increasing complexity in inheritance patterns, associated phenotypes and variability often hampers confirmation of diagnosis and counseling.
Parallel efforts to curate gene disease relationships in NDD exist by different groups and institutions, with varying approaches and definitions. One of these is the expert curated SysID database initially published in 2016. SysID includes both established (primary) and candidate genes and their relation to phenotypes and associated inheritance patterns. With currently 1,454 primary genes (status 10th April 2021) these have nearly doubled in the past 5 years, while the candidate genes have tripled. With the latest update the database contains 3,088 short textual descriptions ("synopsis") about gene-disease relationships. To enable further usage of the database we have now updated dependencies (MySQL, PHP framework, Apache webserver), revised gene and disease names and moved the tool to a new server available to the public at www.sysid.dbmr.unibe.ch.
To facilitate further development and incorporate new curation principles, we now developed SysNDD as a new, succeeding database structure and web tool available at www.sysndd.org. To allow interoperability and mapping between gene-, phenotype- or disease-oriented databases we center our approach around curated gene-inheritance-disease units, so called entities, which are annotated with a predefined list of NDD associated phenotypes (based on HPO). An entity is defined by the combination of a gene (HGNC identifier), a disease ontology term (OMIM or MONDO identifier), an inheritance term (HPO term) and optionally a mutational pathogenicity mode. The SysNDD webtool (programmed in JavaScript using Vue.js) allows browsing of tabular data for NDD entities or genes and filtering by defined HPO phenotypes, thus allowing compilation/download of gene panels and comparison with other curation efforts. Individual pages for entities, genes and diseases provide specific information and links to commonly used resources. Additionally, the data is programmatically accessible through an application programming interface (API; programmed in R using plumber). Currently we are establishing a curation pipeline which will allow a collaborative effort, fueled by the support from the ITHACA network to re-review and update the clinical descriptions of all entities. In summary, we will present the current status of these tools, our analysis based on the compiled data and future development directions like incorporating variant data and machine learning techniques to cluster the "NDD entity space". Our long-term goal is incorporation of the high-quality, manually curated SysNDD data into European and international gene disease relationship databases like the Orphanet ontology thereby improving diagnostics and care for individuals with rare NDDs.

Kosaki syndrome: a new overgrowth syndrome with therapeutic perspectives

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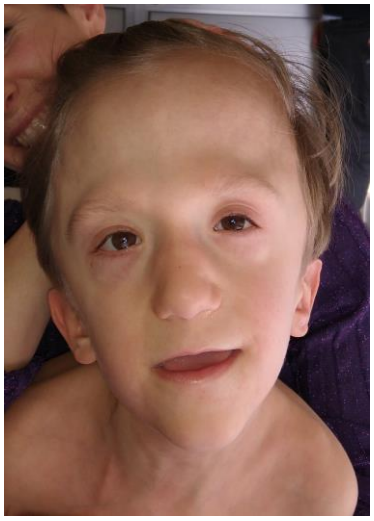
Kosaki syndrome is one of the most recently molecularly characterized overgrowth syndromes, with 11 patients reported worldwide. It is characterized by skeletal overgrowth, hyperelastic skin, scoliosis and progressive neurological decline and it is caused by specific gain-of-function variants in *PDGFRB* gene. The two known types of pathogenic variants (p.(Pro584Arg) and p.(Trp566Arg)) are exclusively located in the juxtaglomerular domain that regulates autoactivation/inhibition of PDGFRB.

Our patient was referred to our service at 5 years of age and presented with syndromic overgrowth and severe neurodevelopmental delay: his height was 120 (>97° percentile, +2.4 SD), the weight 21 kg (80° percentile) and the cranial circumference 53 cm (92° percentile). He had characteristic facial features with prominent forehead, high hairline, hypertelorism, downslanted palpebral fissure, wide nasal bridge, flat philtrum and thin upper lip (see figure 1). At physical evaluation several subcutaneous myofibromas were present (axillary, right thigh, orbital, sternal, palmar) they were histologically defined as part of an infantile myofibromatosis. He furthermore carried a ventriculoperitoneal shunt due to tetraventricular hydrocephalus, had an interventricular cardiac defect and epilepsy treated with Levotiracetam. A previously performed chromosomal microarray analysis was negative. His prenatal history was remarkable from the 22° week of gestational age, when cerebellar vermis hypoplasia and abnormal position of tentorium cerebellum was noticed.



Given the association between myofibromatosis and clinical features suggestive of Kosaki syndrome, Sanger sequencing of the two known variants in the *PDGFRB* gene was asked for and the pathogenic heterozygous variant c.1696T>C, p.Trp566Arg identified.

Recent reports have proposed the use of Imatinib, a tyrosine kinase inhibitor known to downregulate PDGFRB activation, for treatment of patients affected by generalized infantile myofibromatosis and Kosaki syndrome with encouraging results on patients' and caregivers' overall quality of life. We thus proposed the same approach to our family and pleaded for ethics approval in June 2021.

A novel frameshift variant in a patient with CHD8-Related Overgrowth syndrome

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Chromodomain helicase DNA-binding protein 8 (CHD8) is an important transcriptional regulator that mostly expressed in central nervous system functioning in axonal development and neuronal migration. *CHD8* gene was previously associated with autism susceptibility (# OMIM 615032) in the literature but in recent studies patients with distinct phenotype of Overgrowth/Intellectual Disability (ID) syndrome was identified.

CHD8-related Overgrowth syndrome is a rare syndrome consist of mild to moderate intellectual disability, increased height and head circumference (>2SD), autism spectrum disorder, gastrointestinal problems, sleep difficulties, facial dysmorphism, seizures, neonatal hypotonia, pes planus, fifth finger clinodactyly, umbilical hernia, scoliosis and glabellar hemangioma. Facial dysmorphic findings resembled to Sotos syndrome which include, frontal bossing, down-slanting palpebral fissures, high hairline and prominent chin.

Here we report a 20-month-old male patient that was referred to our outpatients' clinics for investigation of facial dysmorphism and neuromotor developmental delay. The parents of the proband were not related and two older siblings were healthy. Prenatal screening tests and anatomical screening during pregnancy was normal. He was born at 34th week by C/S because of maternal cervical insufficiency and was admitted to the NICU for approximately one month. The patient had one seizure due to hypoglycemia in that period and had neonatal hypotonia. His birth

parameters were; weight: 2800gr (90th percentile), height: 48cm (>97th percentile), head circumference: 34cm (97th percentile). Neuromotor milestones of the patient was severely delayed comparing to his peers. He gained his head control around 12 months, sit without support around 15 months, walk around 18 months and speak only with 2 words at the time of the examination. In his intracranial MRI; lateral and third ventricles were dilated, cavum septum pellucidum was detected as structural abnormalities. Ophthalmological examination of the patient revealed bilateral pale optic disc and abnormal changes of the retinal pigmentary epithelium of the fundus. In his physical examination; weight: 13kg (+0,86SD), height: 90cm (+0,99SD), head circumference: 53cm (+2,64SD) were detected. Frontal bossing, frontoparietal bolding, blonde hair, downslanted palpebral fissures, micrognathia, soft, prominent ears, dough-like skin were noted. According to the pathological findings mentioned Sotos syndrome was suspected at the patient initially. Karyotype analysis, *NSD1* gene FISH analysis and *NSD1* sequence analysis were performed and results were normal. Whole exome sequencing analysis was planned and at *CHD8* gene, novel c.4614_4618delAAAGT variant which is classified as ‘‘Pathogenic’’ according to the ACMG classification was detected. This variant was leading to a frameshift at the 1539th position at the aminoasid chain and was generating a truncated protein. Segregation analysis was done to the asymptomatic, healthy parents and relevant variant were shown to be not present. Genetic counselling was given to the parents and inheritance risks due to the germline mosaicism were indicated.
CHD8-Related Overgrowth syndrome is relatively new defined phenotype and less than 100 patients have been reported. To our knowledge our patient is the first Turkish case and also one of the youngest patients that was reported in the literature so far. He manifested the main clinical findings of the syndrome. Despite the fact that he had noticeable developmental delay it was not possible to asses the intellectual disability, behavior abnormalities because of his young age. Neonatal hypotonia, facial dysmorphism resembling Sotos syndrome and macrocephaly (>2SD) were expected features of the syndrome but normal ranged height, absence of the skeletal findings and other rare findings were distinct features.

Male patient with ALG13 associated congenital disorder of glycosylation

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Introduction: Protein N-glycosylation is a post-translational modification with a significant influence on protein function and stability. Disorders of this pathway lead to highly heterogeneous and multi-systemic clinical findings. ALG13 gene localized on X chromosome encodes a highly conserved transferase which catalyzes one of the first steps in the N-glycosylation pathway. Pathogenic variants in ALG13 (particularly variant c.320A>G) are associated with early infantile epileptic encephalopathy (EIEE36) and congenital disorder of glycosylation (ALG13-CDG).
Patient: The index case was born to non-consanguineous healthy Caucasian parents with unremarkable family history. Currently, he is a 4-year-old male, born prematurely at 33rd GW by C-section due to premature rupture of membranes. Physical examination showed the distinct dysmorphic features – bilateral anotia associated with low set rudiments of the ears; plagiocephaly; frontal bossing; wide root and depressed nasal bridge. Other malformations included pectus excavatum, simian crease in the left palm, clinodactyly of the 5th finger and hepatosplenomegaly. Haematological and biochemical examination detected thrombocytopenia and neutropenia. Transferrin isoeletric focusing was normal.
In the first year, the patient presented with necrotizing enterocolitis (with subsequent short bowel syndrome) and several sepses. Intractable epileptic seizures (mainly infantile spasms) developed during 6th month. EEG recording was

significantly abnormal – multifocal discharges above the posterior quadrants while awake and intermittent burst - suppression activity during sleep. Psychomotor development was delayed from birth with subsequent regression to newborn level evident from the age of 6 months (in connection with epilepsy)
Methods: DNA was extracted from peripheral blood lymphocytes by standard extraction procedures (Magcore assay). Whole exome sequencing was followed by bioinformatics analysis utilising the TRIO mode function. Filtration and interpretation of NGS data were performed using the software VarAFT. Sanger DNA sequencing was used for the verification of the detected variant.
Conclusion: Recurrent de novo variant c.320A>G within gene ALG13 has been mainly described in females (34 cases) but only in 2 males. Manifestation of this pathogenic variant in males is slightly more pronounced, especially in facial dysmorphism and hearing loss. The mechanism of the pathogenicity is unclear.
We found this variant in another male patient with developmental delay, epileptic encephalopathy, hearing loss and facial dysmorphism. Manifestation of disorder is consistent with the description of another male patient by Galama et al., 2017.

Session 7: Syndrome delineation single cases

Perching syndrome: clinical presentation of the first african patient

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PERCHING syndrome is an autosomal recessive multisystem disorder characterized by global developmental delay, facial dysmorphism, microcephaly, joint contractures, camptodactyly, respiratory and swallowing difficulties, and poor growth. Additional common features include ocular anomalies, hypotonia, brain imaging abnormalities, seizures, feeding issues, sleep disturbances, and recurrent infections. Each letter of the PERCHING acronym represents 2 important phenotypic elements.

We report the first phenotypic description of PERCHING syndrome in a patient from Central Africa. A one-year-old boy, born prematurely by caesarean and he benefited resuscitated for over 5minutes, was admitted in neonatal intensive care at the University Hospitals of the University of Kinshasa. He presented multiple episodes of respiratory distress postnatally. His development was remained delayed regarding the gross and fine motor development, speech and global hypotonia. Seizures were also observed. Dysmorphism evaluation revealed typical resting posture, microcephaly, short stature, hypotrophia, long face, sparse hair, bulbous nasal tip, smooth philtrum, tented upper lip vermilion, jaw and joint contractures, broad inferior crus of antihelix at left, underdeveloped inferior crus of antihelix at right, everted antitragus, widely intermamillary distance, fingers camptodactyly, absence of right transversal palmar crease, partial bilateral toes syndactyly 2-4.

Duo-based clinical Whole genome Sequencing (proband and unaffected mother) was performed and identified two heterozygous variants in the *KLHL7* gene, including a maternally inherited splice variant c.793+5G>C, classified as a variant of uncertain significance, and a frameshift variant of unknown inheritance, c.944delG (p.Ser315ThrfsTer23), classified as likely pathogenic. Whether the c.944delG (p.Ser315ThrfsTer23) variant was *de novo* or paternally inherited could not be determined from this study, as only the mother was tested.

Variants (Loss-of-function and missense) in *KLHL7* are associated with PERCHING syndrome, which was consistent with the clinical phenotype in our patient compared to those described in the literature.

Keywords: Central Africa, Dysmorphism, *KLHL7*, PERCHING syndrome

ATAD3A variants in two brothers with bilateral congenital cataract

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ATAD3A gene (OMIM: ATPase FAMILY, AAA DOMAIN-CONTAINING, MEMBER 3A, #612316) is part of a 3-gene cluster, along with *ATAD3B* and *ATAD3C*. ATAD3A is an inner mitochondrial membrane protein that interacts with MFN2, OPA1 and DNM1L, suggesting that ATAD3A may be with a role in mitochondrial DNA maintenance and cholesterol metabolism. The gene family has been associated with a diversity of neurological syndromes and with diverse clinical symptoms. These phenotypes include cerebellar hypoplasia, developmental delay, hypotonia, hereditary spastic paraplegia, axonal neuropathy, hypertrophic cardiomyopathy or visual impairment (optic atrophy, cataract, corneal clouding).
Case report: The proband is a second child in family. After birth bilateral cataract was diagnosed and operated at the age of 9 months. Also his elder brother had the diagnosis of congenital cataract and was operated at the age of one year. There is no other similar problem in family, father`s ophthalmological investigation revealed normal findings, mother had slight corneal opacity at the age of 60 years. At the age of 45 years, his height is 179 cm, weight 60 kg, BMI 18.7. He has severe visual impairment, deeply set eyes, strabismus (convergent) and nystagmus with no other health problems.
Results: Trio-based exome sequencing analysis revealed two *ATAD3A* gene variants *in trans*: (1) partial deletion, including exon 1-4 (possible also exon 1-3 or 1-5) of *ATAD3A* gene and also partial deletion of *ATAD3B* gene, inherited from the mother. Similar deletions are previously described as pathogenic; (2) missense variant in *ATAD3A* gene exon 2: NM_018188.4(ATAD3A):c.229C>G p.(Leu77Val) rs138594222, inherited from the father. The missense variant has described as variant of unknown clinical significance (VUS). According ACMG criteria PM2 (rare in gnomAD database), PM3 (locates in *trans* position with pathogenic allele) and PM5 (missense variant p.Leu77Arg in the same position has been described as pathogenic) it is possible to evaluate the variant as likely pathogenic. The affected brother carries also both variants.
Conclusion: We report the family with biallelic variant in *ATAD3A* gene, with congenital cataract as the only clinical symptom. Patient cohort with *ATAD3A* variants is small, thus its phenotypic spectrum may be wider than currently described. The novel missense variant may lead to milder phenotype than usually described in *ATAD3A*-related syndromes.
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Expanding the phenotypic and genotypic spectrum of NFIA-related disorder spectrum

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Brain malformations with or without urinary tract defects (BRMUTD, OMIM 613735) is a rare developmental disorder caused by heterozygous loss-of-function variants in the *NFIA*. The clinical characteristics include structural brain anomalies, macrocephaly, seizures, cognitive impairment, and urinary tract defects.
The *NFIA* gene encodes a member of the nuclear factor I (NFI) family of transcription factors playing an important role in normal development of multiple organs. NFI proteins control the neurodevelopmental processes including axon guidance and outgrowth, glial and neuronal differentiation, and neuronal migration.
We report here a Finnish mother and her two children affected with BRMUTD. All three affected individuals had macrocephaly and occipitofrontal head circumference above 99 percentile, developmental delay, asymmetrically dilated lateral ventricles, strabismus, and hyperopia. Brain imaging showed dilatation of the lateral ventricles and subarachnoid spaces, enlarged perivascular spaces, decreased periventricular white matter, and hypoplastic corpus callosum. Affected mother had a submucous cleft palate and bifid uvula; another affecter daughter had a high narrow palate. Dysmorphic features were a prominent broad forehead, prominent occiput, short nose, tented upper lip, anteverted nares, and small low set ears (Figure 1). Two affected individuals had normal urinary tract and kidney structures. Another affected daughter had left sided congenital ureteropelvic junction obstruction resulting in left kidney insufficiency. Her right kidney structures and function were normal.
Exome sequencing revealed a novel heterozygous *NFIA* c.681del p.(Phe227Leufs*47) variant segregating with the macrocephaly, developmental delay and ventriculomegaly in the family. It is classified as likely pathogenic according to the recommendations of ACMG.
Our findings expand the phenotypic and genotypic spectrum of the *NFIA*-related disorder spectrum and demonstrate the variable clinical phenotype caused by the same pathogenic *NFIA* variant.

Figure 1. Index patient at the age of 1 year (A,B) and at the age of 16 years (C,D) showing facial asymmetry, strabismus, prominent occiput, prominent broad forehead, small low set ears, depressed nasal bridge, anteverted nares, and tented upper lip. MRI scan taken at 6 years of age showing hypoplastic corpus callosum (E). (Written informed consent was obtained for the publication of figures.)

Reverse phenotyping in a patient with a novel pathogenic variant in *FBX011* gene

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We describe an 8-year-old boy, who is the first son of healthy, non-consanguineous parents. Irrelevant family history and uneventful pregnancy and delivery.

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At the age of 4 months, postnatal microcephaly, ophthalmological features (including right microphthalmia, athalamia, nuclear cataract with posterior synechia, right horizontal nystagmus, and strabismus), mild acral anomalies, hypotonia, and mild developmental delay were noticed. Cerebral MRI revealed atrophy of the prechiasmatic segment of the right optic nerve. He evolved with aggressive behavior, attention deficit disorder, and moderate intellectual disability (ID), affecting mostly language, fine motor skills, and motor coordination.
On physical examination, he presented some facial dysmorphisms (Fig. A), namely facial asymmetry, thin eyebrows, upslanting palpebral fissures, bulbous nasal tip, prominent left ear, thin upper lip, retrognathia, puffy and tapered fingers with clinodactyly of the fifth finger, sandal gap, deep sole creases, clinodactyly of the second toe bilaterally, and a slightly broad hallux.
CMV infection was excluded, and extensive neurometabolic investigation was also negative. Array-CGH (*Comparative Genomic Hybridisation, CGX-HD 180K, Signature Genomics, PerkinElmer*) was normal. Based on the clinical picture, pathogenic variants in *KIF11, CREBPP* and *EP300* were initially excluded. Trio whole exome sequencing (WES) was performed in 2018, and did not identify any variants that could explain the phenotype. The mother being pregnant, trio WES reanalysis was perfomed in 2021 in the attempt to reach a diagnosis, and revealed the presence of a novel *de novo* heterozygous pathogenic variant in *FBX011* gene: c.1166dup, p.(Cys390Metfs*3).
Pathogenic variants in *FBX011* gene cause IDDFBA (Intellectual Developmental Disorder with Dysmorphic Facies and Behavioral Abnormalities, *OMIM#618089*). To our knowledge, only 24 cases have been reported in the literature so far. All patients presented ID of variable degrees, and many shared behavioral problems and ophthalmological anomalies, such as optic nerve hypoplasia. Although a typical gestalt cannot be established yet, our patient´s facial features are consistent with the literature.
This case illustrates the advantages of WES reanalysis in achieving a molecular diagnosis in syndromic ID patients, and highlights the value of reverse phenotyping in the interpretation of novel variants in the clinical setting.

Fig. A - Our patient at 1y; 1y and 5mo; 3y and 6y (left to right).

A homozygous missense loss-of-function variant in amyloid-beta precursor protein (APP) may cause severe intellectual disability

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Intellectual disability is a clinically and genetically heterogeneous group of disorders. Recent advances in genetic new technologies, particularly with an easier access to whole exome or genome sequencing, has allowed the identification of an increasing number of genes involved in neurodevelopment disorders, either genes not yet known to be associated with a human condition or genes already known for causing totally different disorders. In the latter case, interpretation of the variant(s) identified may be challenging. Here we report the identification of a homozygous missense variant in the gene coding the amyloid-beta precursor (*APP*), in which heterozygous gain of function mutations are known to cause familial early-onset Alzheimer disease, in a patient with severe intellectual disability, epilepsy, and behavioural problems.

The patient was the first child of healthy Moroccan parents who are related (their fathers are half-brothers). There was no previous family history and his two sibs, a boy and a girl, had no developmental problems. The patient was born at term following a normal pregnancy. Delivery was uneventful and birth parameters were normal. The patient had global psychomotor delay and autistic features. He developed absence epilepsy at the age of 8 years. On last examination at the age of 12, he had severe intellectual disability (had no speech, was not toilet-trained) and had marked behavioral problems, but neurological examination was normal. Physical examination did not reveal any dysmorphic features. The head circumference was at +2.5 SD, and the stature was 2 SD above the expected height. Vision and hearing were normal. Abdominal ultrasound did not reveal congenital malformations. Brain MRI was normal except for some degree of cortical atrophy. As all routine genetic investigations (chromosome analysis, *FMR1* analysis, array-CG), as well as exome sequencing and a wide metabolic screening had given normal results, a whole genome sequencing was performed. This showed a homozygous missense variant NM_201414.3: c.440A>G:p.(His147Arg) in the E1 domain of the amyloid-beta precursor protein. Both parents were heterozygous for the variant.

APP is a ubiquitous cell surface receptor able to cis- or trans-dimerize with APLP. The most studied isoform of APP is the 695 amino acid protein which is expressed at the surface of the neurons. It has been observed that APP dimerization at the neuron membrane participates to neurite growth, neuronal adhesion, axonogenesis and synaptogenesis. Many pathogenic missense gain-of-function variants have already been identified in the Aβ domain and are associated with the accumumation of amyloid β peptide leading to early onset Alzheimer disease. To date, only one homozygous loss-of-function variant in *APP* has been reported, in an individual affected with global developmental delay, epilepsy and microcephaly (Klein *et al*. 2016). The missense variant we have identified substitutes a cupper-binding histidine that is required for APP dimerization. We are currently trying to modelize the functional effects of this variant in HEK293 and SH-SY5Y cells. Further descriptions of patients may help to confirm the implication of biallelic loss-of-function *APP* variants in intellectual disability.

Session 8: Miscellaneous

Trisomy 8 and NIPT: a challenge

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Non-invasive prenatal testing (NIPT) was originally developed to detect common fetal aneuploidies involving chromosomes 13, 18 or 21. However, rare autosomal trisomies (RATs) are a relatively frequent secondary finding, detected in approximately 0.23% of genome-wide cfDNA analyses. The relative frequency of trisomy 8 among RATs detected by NIPT lies close to 9%. Given that complete trisomy 8 usually results in an early miscarriage, most cases are mosaic, resulting from postzygotic non-disjunction. Interpretation of these data is challenging, due to some specific characteristics of trisomy 8 mosaicism. First, some cases of trisomy 8 detected by NIPT may be of maternal origin. This can be due to low-grade maternal mosaicism without phenotypic manifestations. The result may also point to an occult maternal malignancy, as trisomy 8 is a common chromosomal abnormality in hematological cancer of the myeloid cell line. Besides, it has also been described in certain solid tumors and in rare cases of non-Hodgkin lymphoma. Second, trisomy 8 cases that do not involve the trophoblast will not be detected by NIPT. This is true for type II (confined placental) and type V (true fetal) mosaicism, where trisomic cells are restricted to the mesenchymal tissue. These two subtypes of mosaicism account for about 79% of all trisomy 8 cases picked up by chorion villus sampling and will inherently remain undetected by NIPT. Third, a proportion of at least 11% of true fetal trisomy 8 mosaicism is missed by amniocentesis. Therefore, it could prove useful to perform fetal blood sampling in cases where the results of NIPT and amniocentesis are discordant or when prenatal ultrasound shows aberrant features. Furthermore, the percentage of mosaicism in amniocytes does not reliably predict the clinical outcome. However, the level of mosaicism in fetal blood cells is significantly greater in cases with an abnormal outcome, which is an additional motivation to consider fetal blood sampling.

Here, we illustrate the pitfalls of NIPT and amniocentesis in the detection and interpretation of trisomy 8 by reviewing five relevant clinical cases from the University Hospital in Leuven. Since 2013, we detected 3 cases of trisomy 8 on NIPT that proved to be of maternal origin. Two trisomy 8 NIPT results were due to low-grade maternal mosaicism. In the third case subtle genome-wide chromosomal aberrations with a predominant gain of chromosome 8 were seen on cfDNA analysis. Three years later, this woman was diagnosed with primary mediastinal large cell B-cell lymphoma, with a congruent profile of chromosomal anomalies between tumor DNA and cfDNA suggesting a potential link. We then present one case of true fetal trisomy 8 mosaicism that was missed by NIPT and illustrates non-involvement of the trophoblast. The last case described here is an example of a false negative amniocentesis after trisomy 8 detection on NIPT, underscoring the potential added value of fetal blood sampling.

We hope that this work will enhance the awareness and understanding of the difficulties in interpreting trisomy 8 mosaicism from prenatal testing and aid clinicians in determining their counselling approach.

Thalidomide embryopathy. Forgotten but not gone

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Thalidomide embryopathy is probably the best known example of a teratogenic disorder. Use of thalidomide during the first months of pregnancy will result in a recognizable pattern of congenital malformations, mainly in the limbs, ears and heart. This condition was first recognized in the nineteensixties in Europe, and thalidomide was withdrawn from the market. However, thalodimide is en effective drug for the treatment of several conditions including erythema nodosum leprosum. Even nowadays, children affected with thalidomide embryopathy are still being born. Most Western European doctors do not evaluate the possibility of thalidomide embryopathy in the differential diagnosis of limb defects, due to the accepted dogma that fetal exposition to thalidomide has not been possible after thalidomide was withdrawn from the market.
We discuss the diagnosis of thalidomide embryopathy in a series of patients that presented in our department recently in order to obtain legal recognition of their condition.

Reanalysis of SNP analysis data in patients with neurodevelopmental delay

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The number of genes known to cause intellectual disability is increasing every year. In the past 6 years, about 500 new genes were discovered to cause intellectual disability.
This has implications for the diagnostic process in neurodevelopmental delay (NDD). After a negative result it pays off to run a re-analysis after some time. Indeed several groups have studied the yield of re-analysis of WES-data for several indications, reporting a mean yield of ~15%.
The growing knowledge about disease-causing genes also has implications for the interpretation of Copy Number Variants (CNVs). Around 20% of individuals with intellectual disability have a CNV, in a total of 10-12% this CNV is classified as likely pathogenic. This leaves a substantial number of (de novo) CNVs with unknown significance.
Our laboratory switched from karyotyping to CNV analysis in 2008, and has since collected a series of ID patients with de novo CNVs that could not be classified.
A recent case of re-classification of a de novo CNV as pathogenic, made us realize that the growing knowledge about disease-causing genes also has implications for CNVs. This led us to study all ID patients between 2008-2013 with a de novo CNV (n=107). We re-evaluated CNVs with the label *possibly pathogenic* or *unlikely pathogenic* by checking location and gene content in both PubMed and DECIPHER.
In 50% of cases we found recent publications about the CNV. We could re-classify previously unclassifiable variants in 17% of patients. In 7% this had clinical consequences (e.g. screening advise).

We will present our data collection and show clinical examples of re-classified CNVs.

10 years' experience in the search of a probable genetic condition among children (S Milena)

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Introduction: Genetic disorders are becoming a pronounced part of the routine clinical practice. It is estimated that rare diseases, which are mostly genetic in essence, actually affect million people worldwide. Hence, having patients with a genetic disorders is not exclusive to the genetic counselors, but could be considered a part of the routine clinical practice. The aim of the study is to present our experience in establishing the diagnosis in children with a probable genetic condition for a 10-year period.
Materials and methods: Retrospective analysis of pre- and post-test genetic counselling, clinical evaluation and/or genetic analysis was performed. A total of 938 children, presenting with single/multiple congenital anomalies and/or facial dysmorphism and/or developmental delay, were included.
Results: 259 (26.6%) patients were diagnosed with a certain genetic condition. Of them 84 (32.4%) -with monogenic disease, 34 (13.1%) - with microdeletion/duplication or imprinting syndrome, 45 (17.4 %) - with chromosomal aberrations. Additionally, in 96 (37.1%) children diagnosis was accepted based on the specific phenotype in absence of genetic confirmation. All of the diagnoses refer to the group of rare or ultra-rare diseases and this incorporates one of the major obstacles to reaching the correct diagnosis. Nevertheless, some characteristic facial features can be a key to the achievement of this goal (tab. 1).

Hutchinson-Gilford progeria Beare-Stevenson cutis gyrate Achondropalasia LEOPARD Bardet-Biedl Fanconi anemia Nijmegen breakage	Cartilage-hair hypoplasia Cornelia de Lange Cardio-facio-cutaneus Noonan Mowat-Wilson Greig cephalopolysyndactyly Osteoporosis – pseudoglioma Jansen de Vries

Table 1. Confirmed genetic syndromes with facial dysmorphic features as a leading symptom

Because of the technical and financial limitations, conventional cytogenetics has been the leading method for diagnosis, especially in the first part of the analyzed period. However, with the expansion of the high-resolution molecular tests, including aCGH, MLPA and sequencing, the percentage of confirmed genetic disorders increases predominantly in the recent years.
Conclusion: Despite the growing availability of genomic diagnostic tests, many children with suspected genetic diseases remain undiagnosed. However, with the decreasing cost and increased availability of new technologies, together with the increasing experience of the clinical geneticists, genetic diagnosis is becoming a more and more reachable aim.

Translational diagnostics program, an innovative hospital approach to genetic diagnosis of rare neurodevelopmental disorders

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INTRODUCTION: There is a need to find the etiological diagnosis for managing and treating patients with undiagnosed and rare diseases (URDs). In a significant number of patients, genome sequencing has increased the rate of diagnosis of neurodevelopmental disorders, but it also detects genetic variants of unknown clinical significance (VUS) or inconsistent with the phenotype. To assist physicians in the variant classification concerning patient's phenotype we have developed the hospital intramural Translational Diagnostics Program (TDP)[1].
OBJECTIVES: To validate for diagnosis variants that are classified as a VUS or novel phenotype-genotype correlation using the holistic approach "precision phenotyping – clinical genomics – functional genomics – team decision-making".
RESULTS: Between 2017 and 2020, we conducted 4,149 clinical exome sequencing studies at the Department of Genetic Medicine at Sant Joan de Déu Children's Hospital. The genetic diagnosis was achieved in 1,360 patients (33%) and in 717 (17%) we detected genetic variants classified as VUS following the ACMG/AMP standards and guidelines. To address functional studies of a VUS or a phenotype-genotype incongruity we applied the TDP pipeline that includes: (1) a comprehensive evaluation of the phenotype, including HPOs; (2) in silico analysis of the pathogenicity of the candidate genetic variant/s; (3) functional validation of the variant by examine the encoded protein using molecular and cellular assays, and comparative computational analysis of confocal microscopy images; (4) diagnostic decision-making with referring physicians.
Currently, 21 patients with a syndromic neurodevelopmental disorder have been admitted in the TDP for biological validation of the candidate genetic variant/s. We confirmed in 12 out of 21 patients a deleterious impact of the VUS upon the location/function of the encoded protein. Of the remaining patients, in three cases, the variant had no functional impact on the coded product, five are under study, and one are still under discussion.
CONCLUSIONS: The genetic diagnosis of URD and neurodevelopmental patients requires the promotion and implementation of intramural functional genomics/diagnostics programs to support and resolve medical problems when the patient's variant is uncertain or inconsistent with the phenotype. The TDP is a strong in-house tool to fill the gap between phenotype and genotype.
[1]Pijuan et al. *J Mol Diagn* 2021, doi:10.1016/j.jmoldx.2020.10.006.

Familial cleft tongue caused by a unique translation initiation codon variant in *TP63*

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Mutations in transcription factor p63 have been linked to several autosomal dominantly inherited malformation syndromes. These disorders show overlapping phenotypic characteristics with various combinations of the following features: ectodermal dysplasia, split-hand/foot malformation/syndactyly, lacrimal duct obstruction, hypoplastic breasts and/or nipples, ankyloblepharon filiforme adnatum, hypospadias and cleft lip/palate. We describe a family with six individuals presenting with a striking novel phenotype characterized by a furrowed or cleft tongue, a narrow face, reddish hair, freckles and various foot deformities. Whole-exome sequencing identified a novel heterozygous variant, c.3G>T, in *TP63* affecting the translation initiation codon (p.1Met?). Sanger sequencing confirmed dominant inheritance of this unique variant in all six affected family members. In summary, our findings indicate that heterozygous variants in *TP63* affecting the first translation initiation codon result in a novel phenotype dominated by a cleft tongue, expanding the complex genotypic and phenotypic spectrum of *TP63*-associated disorders.

Session 9: Rasopathies

Alteration of mitochondrial proteostasis and bioenergetics in Costello syndrome

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Germline mutations that activate genes in the canonical RAS/MAPK signaling pathway are responsible for rare human developmental disorders known as RASopathies. Here, we analyzed the molecular determinants of Costello syndrome (CS) using a mouse model expressing $HRAS^{G12S}$, patient skin fibroblasts, hiPSC-derived human cardiomyocytes, a $HRAS^{G12V}$ zebrafish model and human fibroblasts expressing lentiviral constructs carrying $HRAS^{G12S}$ or $HRAS^{G12A}$ mutations. The findings revealed alteration of mitochondrial proteostasis and defective oxidative phosphorylation in the heart and skeletal muscle of Costello mice that were also found in the cell models of the disease. The underpinning mechanisms involved the miR-221*-dependent inhibition of AMPKα2 expression and the concomitant alteration of LKB1 activation by mutant forms of HRAS, leading to alteration of mitochondrial turnover and bioenergetics. Pharmacological rescue of mitochondrial proteostasis restored organelle bioenergetics in $HRAS^{G12A/S}$ cell models, reduced heart mass in CS mice and reduced the occurrence of developmental defects in the CS zebrafish model.

Novel 10-nucleotide deletion in *HRAS* gene in a girl with clinical features consistent with Costello syndrome

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Heterozygous, mostly de novo, activating germline pathogenic variants in the proto-oncogene *HRAS* represent an established cause of Costello syndrome (CS), which is one of the rarest types of RASopathies. Individuals with CS usually present with characteristic findings affecting multiple organ systems, including cardiac involvement and increased risk of malignancy. The phenotypic spectrum is wide, ranging from mildly affected patients to patients with severe phenotype with early lethal complications (1). The majority of *HRAS* pathogenic variants are missense changes affecting codons 12 or 13 (2). We report on a 2-year old girl with *de novo* 10-nucleotide deletion in *HRAS* gene (c.488_497delTCTGGGACCC, NM_176795.4; p.Leu163ProfsTer52, NP_789765.1), who presented with feeding difficulties and failure to thrive in infancy, relative macrocephaly, hypotonia, joint laxity, global developmental delay, coarse facial features and sparse, fine hair. Listed clinical features are consistent with CS phenotype. No additional major abnormalities were seen on ultrasound of the head, heart, and abdomen, done in the neonatal period. By our knowledge, only one clinical case of an individual with similar phenotype and partially overlapping 10-nucleotide deletion in *HRAS* gene (c.481_490delGGGACCCTCT, NM_176795.4), which causes the same change in the protein structure (p.Leu163ProfsTer52, NP_789765.1), has been described so far. Molecular and biochemical studies in this case demonstrated a new mechanism leading to altered *HRAS* function (2). In conclusion, we report on a second case of a patient with 10-nucleotide deletion in *HRAS* gene (partially overlapping with previously described 10-nucleotide deletion), which further confirms that not only missense variants, but also some specific deletions in *HRAS* gene can lead to CS overlapping phenotype.

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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

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We report a 7 year-old child with diffuse epidermal nevi on the face and head, right upper limb, thorax, left lower limb, arranged according to Blascko's lines, who developed a left paratesticular embryonic rhabdomyosarcoma at 18 months of age. We used NGS custom panel approach to scan the lesions-associated genomic events using blood, buccal brush, fibroblast and rhabdomyosarcoma tissue samples. Parallel sequencing analysis identified a somatic pathogenic gain-of-function variant (c.37G>C, p.Gly13Arg) in the *HRAS* gene in both epidermal nevus and tumor tissues. 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. The variant was absent in the DNA extracted from the proband's peripheral blood and buccal brush, indicating its postzygotic origin. 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. 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. Somatic activating mutations of the *HRAS* gene are associated with various neoplasms. Our findings are in line with previously collected data documenting the occurrence of gene dosage events involving activating *HRAS* alleles in cancers occurring in patients with Costello syndrome. This diagnosis will permit adoption of screening measures in the patient to detect malignant transformation at early stages.

Diagnostic Odyssey in a Chinese patient with Rasopathy

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Introduction. Noonan syndrome (NS) is a rasopathy, a genetically heterogeneous condition, which is characterized by characteristic faces, short stature, congenital heart defect, and developmental delay of variable degree. Pathogenic variants for NS have been found in multiple genes encoding the RAS/MAPK pathway. The clinical presentation is highly heterogeneous. Noonan syndrome with loose anagen hair (NS-LAH) is a subgroup with features of NS but also growth hormone deficiency, distinctive hyperactive behavior that improves with age in most, hair anomalies, e.g. easily pluckable, sparse, hair (loose anagen hair), darkly pigmented skin with eczema or ichthyosis. Classically it is caused by a single recurrent missense *SHOC2* mutation. SHOC2 forms a complex with protein phosphatase 1 (PP1C) which controls activation of signaling proteins such as mitogen activated protein kinases of RAS/MAPK pathway. In 2016, protein phosphatase 1 catalytic subunit beta (PPP1CB) gene has been found to be associated with Noonan syndrome-like disorder with loose anagen hair syndrome (NSLAH2).It is extremely rare syndromal entity featured by macrocephaly, prominent forehead, low-set and posteriorly rotated ears, and developmental delay and anagen hair. Up till now, less than 20 patients had been reported worldwide. Here we report the first case of NSLAH2 in Hong Kong. Case report. The proband presented to clinical genetic service for short stature and dysmorphism at the age of 16 years old. He was born full term in China to a non-consanguineous Chinese couple. Antenatal was uneventful. Physical examination revealed body weight and body height at 3rd centile and relative macrocephaly (head circumference at

97th centile). He had severe hypertelorism, arching eyebrows, bilateral ptosis, hypermetropia, low set ears, pectus excavatum, coarse hair, neck webbing and joint and skin laxity (Figure 1). His cardiovascular examination revealed systolic murmur. He had borderline developmental delay. In view of his presentation, Noonan syndrome /rasopathy was suspected. PTPN11 sequencing and further sequence analysis of related twelve genes (*BRAF, CBL, RASA1, HRAS, KRAS, MAP2K1, MAP2K2, RAF1, SPRED1, RIT1, SHOC2* and *SOS1*) were negative at the age of 17 and 18 years old respectively. Due to high suspicion of rasopathy and possibility of new genes discovery with times, at a follow up visit 5 years later, WES showed a de novo variant c.146C > G (p.Pro49Arg) in *PPP1CB*, which encodes for an important component of the Ras/MAPK signaling pathway (figure 2). The diagnosis of Noonan syndrome-like disorder with loose anagen hair syndrome (NSLAH2) was substantiated. The mutation was de novo. Prenatal diagnosis and pre-implantation genetic diagnosis can be provided to him for reproductive option.

Conclusion. This is the first patient in Hong Kong reported to have molecular confirmed NSLAH2. The phenotypic spectrum is wide for Noonan syndrome. Pattern recognition is important. The diagnostic odyssey illustrated the constant review of clinical phenotype and updating latest genetic discovery in different disease entities are essential in arranging appropriate genetic test to confirm the diagnosis.

Session 10: Short reports

How many mutations are necessary for diagnosis?

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We present the case of a patient in whom we detected two heterozygous de novo variants in two distinct genes which are not related to the clinical abnormalities of the patient. This raises the question of how many mutations are necessary for a definite diagnosis.
We report on a male patient who was first presented to us for dysmorphic consultation on day 11 of life with respiratory distress disorder, bell-shaped thorax, nephropathy with conspicuous renal cortex and several abnormalities in the cranial sonography.
The pregnancy of the mother was initially unremarkable. In the 30th week she had a preterm rupture of membranes. The patient was born in 30+1 via C-section. Directly after birth, he developed respiratory distress and required ventilation. Additionally a pronounced muscular hypotonia in the first days of life was noticeable. The cranial sonography showed a dilation of the lateral ventricles and reduced gyration (pachygyria). Abdominal ultrasound revealed a mild pancreatic hypertrophy and dysplasia of the renal cortex. The dysmorphic examination revealed broad sunken nasal bridge, hypertelorism, slight auricular dysplasia, short fingers (clinodactyly) and big toes with sandal furrow *(see figures 1-3)*.
To determine the cause we carried out a clinical exome analysis (~ 5230 genes). The molecular analysis revealed two heterozygous de novo variants: p.Arg232Cys in the *SLC2A1* gene and p.Arg2139Ter in the *CACNA1A* gene. Both are linked to epileptic-disorders.
SLC2A1 gene (OMIM-G: 138140) is linked to GLUT1 deficiency syndrome-1 (OMIM-P: 606777) which causes infantile-onset epileptic encephalopathy associated with delayed development, acquired microcephaly, motor incoordination and spasticity. Liquor puncture (LP) confirmed the diagnosis in the patient. He is being treated with a ketogenic diet with good response.
CACNA1A gene (OMIM-G: 601011) is linked to developmental and epileptic encephalopathy 42 (OMIM-P: 617106) and Spinocerebellar ataxia 6 (OMIM-P: 183086).
The now 2-year-old patient shows global developmental delay, hypotonia, hypoplasia of the thorax, polysplenia, nephropathy, secondary macrocephaly and facial dysmorphic features but no sign of an epileptic-disorder. EEG is normal and there have been no seizures in the patient's history.
Both detected variants in *SLC2A1* and *CACNA1A* are related to epileptic-disorders and cannot fully explain the abnormalities of the patient. To further determine a genetic cause we carried out a trio WES (~19433 genes). No additional mutation that could explain the patient's phenotype was found.
In summary this case highlights the importance of a detailed genotype/phenotype correlation. In this patient two de novo variants do not correlate with the presented phenotype. This might suggest that a third variant is responsible for the patient's abnormal development or that it's a polygenic disorder. To further investigate a WGS might help solve the presented case.

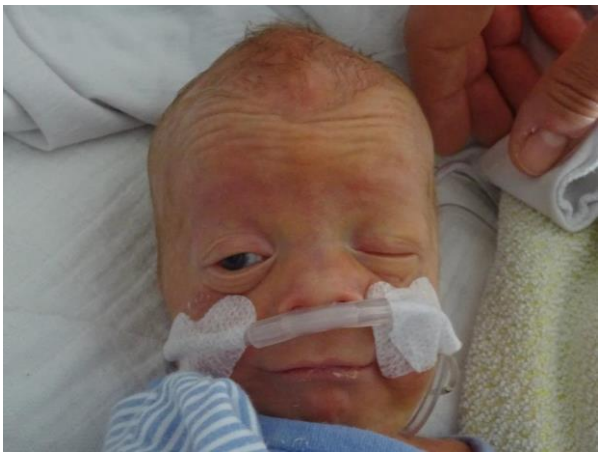

figure 1

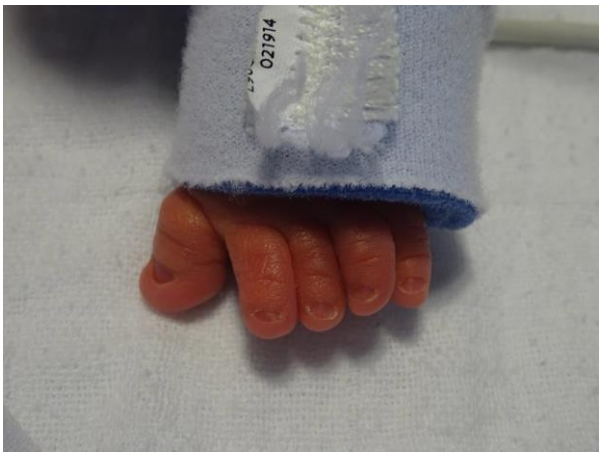

figure 2

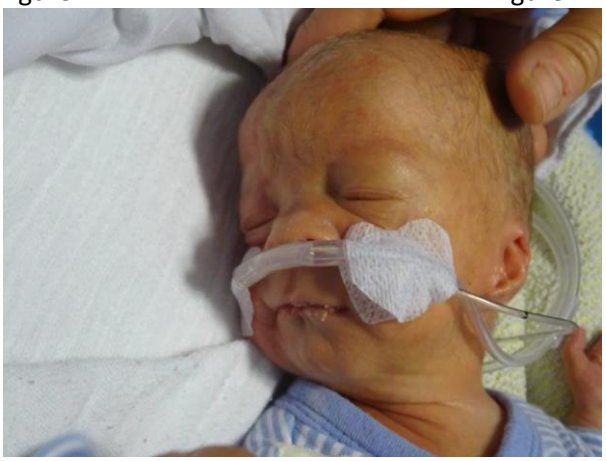

figure 3

Unsolved case: Intellectual deficit with marked facial dysmophism, abducent paresis

Presenter: Katalin Szakszon

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The patient is the second child of healthy, well-educated, non-consanguineous parents, their first child is a girl, who is healthy.
He was born in the 36th week of gestation, with C-section, due to nonresponding NST (non-stress test). Birth weight was 2870 g (50-75pc), length 47 cm (3pc), OFC 32 cm (25-50 pc). Abducent paresis was noted early on, the mom had the same, she needed an opus to correct her strabism. Other than strabismus, the patient has hypermetropia (+5D), epicanthus, vertically narrow palpebral fissures, lacrimal duct stenosis. No epilepsy, no cardiac defect, no intracranial brain malformation (he had a very mild dilatation of the posterior horn of the lateral ventricles prenatally, but the postnatal MRI did not describe anything pathological.)

Puffiness of the back of the hand and feet were remarkable from early age and is still present, the fingers are distally tapering and there are hypoplastic nails on the toes. He had cryptorchism, had an op., and the genitals are normal now.
The facial dysmorphism is striking, there are vertically narrow palpebral fissures, flat supraorbital ridges, sparse, vertically broad eyebrows, convergent strabismus, a broad nasal base, long columella, cupid bow-shaped upper lip, open mouth and large chin. There is severe intellectual disability, developmental delay, attention deficit. He is able to sit and pull himself up standing, he cannot walk yet. At age 3 years, height is 86.5 cm (3pc-2cm), weight (3pc-4kg), OFC is 47 cm (3pc).
Array CGH and Whole exome sequencing resulted negative.
Full facial photographs without covers will be presented during the session, with parental consent.

Unsolved case

Presenter: Milena Stoyanova

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Medical history

- A 9 years old boy from 1st complicated pregnancy (preeclampsia), delivery at 36 weeks by caesarean section, birth weight 3150g, length 48 cm, head circumference 32 cm; Apgar score 6-7, prolonged icterus, muscle hypotonia.
- After birth - facial dysmorphism, complete cleft palate (surgically corrected at 9 months of age)
- No familly history for inherited diseases and consanguinity
- Developmental delay, moderate intellectual dysability
- Speech and language impairment
- Short stature (< 3rd percentile)
- Recurrent ear infections
- Inguinal hernia (surgically corrected at 7 years of age)

Dysmorphic features:

- Downslanted palpebral fissures, ptosis
- Exophthalmos
- Highly arched eyebrows
- Low set ears
- Macroglossia
- Open mouth appearance
- Mandibular prognathia
- Widely spaced teeth
- Hair on the front of the neck
- Pectus excavatum
- Scoliosis
- Unilateral criptorshidism
- Shawl scrotum
- Brachidactily with clinodactily
- Pes planus
- Unsteady gait
- Joint laxity

Investigations

- Routine biochemistry, hematology, hormonal profile : normal
- Echocardiography : ASD- type foramen ovale
- Abdominal ultrasound: reduced parenchyma in the upper right kidney pole
- CT scan of the head : normal
- Hand X-ray: the bone age is adequate for the chronological age
- Cytogenetic analysis: normal male karyotype 46.XY
- Array CGH: normal result

Discussed diagnoses:

- Kabuki syndrome – targeted panel tested – negative for pathogenic mutations in KDM6A, KMT2D
- Ciliopathies Panel -

A2ML1 c.3086G>C (p.Arg1029Pro) heterozygous - VUS ?
AHI1 c.11-9C>A (Intronic) heterozygous - VUS (not likely)
RSPH1 c.471C>G (p.His157Gln) heterozygous - VUS (not likely)

- Aarskog syndrome

The hard differential diagnosis of ectodermal dysplasias

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We describe a 18 years old male from a family with multiple consanguinity. Similar clinical features are reported in the mother and in a first-degree cousin (not examinable). He was born at 35th week of gestation. No other information are available regarding pregnancy and perinatal period.
He was evaluated because of characteristic clinical features. At 18 months cone-shaped teeth were noticed, together with mild umbilical hernia and interatrial defect. Later he was followed for growth delay, hypodontia and hair prone to fall. Mild heat intolerance is referred. A psychometric evaluation found borderline cognitive competence, at least in part due to social conditions. At clinical examinations he showed: multiple dental agenesis, cone-shaped teeth, hypo-agenesis of right pectoral muscles, metatarsal shortening of the IV ray and mild metacarpal shortening of the III-IV-V rays, peculiar facies.
Sanger sequencing and MLPA of the *ED1, EDAR, EDARADD* and *WNT10A* genes were normal. CGH-array and WES filtered for genes related to ectodermal dysplasias are ongoing.
We point out the difficult differential diagnosis of ectodermal dysplasias.

Unclassified facial dysostosis, “atypical” vascular eds, both or none?

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Case report: we evaluated a 6-year-old boy, the second child of unrelated healthy Caucasian parents, born late-preterm with bilateral membranous choanal atresia.
He showed upslanting palpebral fissures; wide and prominent nasal bridge with apparent ocular hypertelorism; prominent eyes (the distance between the supraorbital ridge and the free margin of the upper eyelid is

increased, vaguely as in FGFR-related craniosynostoses); minimal lagophthalmos; orbital region asimmetry mainly due to the left inner canthus being wider (colobomatous?) and displaced downward compared to the right one, with deficient left lower eyelid and ipsilateral scleral show; marked malar flattening; low insertion of columella; short and smooth philtrum; thin and straight upper lip; long ears are (not protruding). Features of the upper lip (thin and straight vermilion, short and smooth philtrum) were in common with his mother. Eyelashes seemed normal. Genitalia are normal (w/ slight phimosis).
He had frequent epiphora and recurring conjunctivitis/blepharitis in both eyes for the first 4-4.5 years of life (dacryostenosis and/or everted lacrimal puncta? dacryocystography not done). A couple of supernumerary maxillary teeth have been removed at 2 and 5 years.
At birth, preoperative CT scan had confirmed atresia and had shown normal semicircular canals and ossicular chains. Brain MRI had shown a large asymptomatic arachnoid cysts in the left temporal fossa. Echocardiogram showed no abnormalities.
Somatic growth was normal. The boy had neither hearing nor vision loss. Sligth hyperfunction of the inferior oblique muscle of the left eye was reported. Although speech onset and development was delayed (as in his sister), language became normal after a short course of S&L therapy. Other developmental milestones were attained on time and psychometric assessment resulted in normal scores.
His father suddenly died of acute myocardial infarction at 48 years. Pregnancy history (including details on teratogenic exposure) and remaining family history were apparently non-contributory.
aCGH showed a paternally inherited 350-kb 11p15.4 microdeletion of uncertain significance, with no clues to any causal links to clinical findings. NGS panel for selected craniofacial disorders (*B3GALTL, CHD7, DHODH, EDN1, EFTUD2, EYA1, FGF10, FGFR2, FGFR3, GJA1, GNAI3, NFIX, PLCB4, POLR1C, POLR1D, SALL1, SALL4, SEMA3E, SF3B4, SIX1, SIX5, TCOF1, TFAP2A, TSHZ1*) and *TXNL4A* Sanger sequencing were normal. Clinical exome sequencing revealed a likely pathogenic *COL3A1* variant of paternal origin.
Conclusions: we report about an unsolved case of putative facial dysostosis of unspecified type (3 out of 5 clinical criteria from *Trainor et al. Am J Med Genet C. 2013 Nov;163C(4):283-94* and positive second opinion from Prof Dagmar Wieczorek) concomitant with an "incidental" *COL3A1* variant that is at "high risk" based on molecular features but whose role is unclear: diagnostic of vascular EDS, unrelated to facial dysostosis or replacing that diagnosis? novel molecular cause of facial dysostosis (without vEDS)? false positive?

Male genital abnormalities in Clinical genetics, a quizz

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Micropenis is a rare condition affecting 1,5/10000 males. It is described in many conditions associated with hypogonadotropic hypogonadism such as Kallmann syndrome, pituitary hormonal defects, Prader-Willi syndrome and ciliopathies. It can also be the result of primary hypogonadism resulting from anorchia, gonadal dysgenesis, Klinefelter, LH receptor defect or testosterone steroidogenesis. Primary hypogonadism is also described in Noonan syndrome, ciliopathies and Trisomy 21. Other causes of micropenis are testosterone activation defects (growth hormone deficiency, androgen receptor defect, 5-alpha reductase deficiency and fetal hydantoin syndrome), developmental abnormalities (penis agenesis, cloacal exstrophy) and syndromic micropenis. (Hatipoglu et al. 2013) More than 280 diseases are associated with micropenis (HPO)
Hypospadia is a much more frequent condition affecting 1/300 males characterised by incomplete fusion of the urethral fold. Its origin is most of the time idiopathic/multifactorial. A rise in prevalence was noted in the last

50 years and could be attributed to drug and chemical exposure, eg : Progestin, dydrogesterone, clomiphene, ibuprofen, venlafaxine, endocrine disruptors, valproic acid... (Foren et al.2021) For isolated hypospadia, genetic risk factors are suspected since familial forms represent 5-10% of cases. A bit less than 400 diseases are associated with hypospadias (HPO).
During this talk, we will present a quizz with different syndromes (old and new) associated with micropenis, hypospadia and other genital anomalies

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J Pediatr Urol. 2021 Jan 21;S1477-5131(20)30746-4
The Human Phenotype Ontology in 2021, Nucleic Acids Research, Volume 49, Issue D1, 8 January 2021, Pages D1207–D1217

Session 11: Dual diagnosis

DeSanto-Shinawi Syndrome in a 3 year-old child with psychomotor development delay and CMT1A disease

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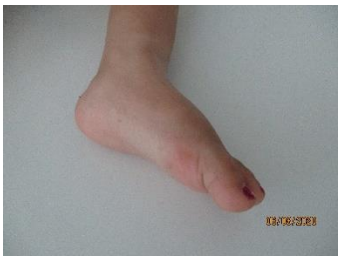
We report a 3 year-old daughter of consanguineous parents who presented with motor development delay, congenital foot deformity, mild facial dysmorphisms, speech delay, unilateral renal agenesis, microcephaly, unspecified hearing impairment, unspecified vision impairment, growth delay and mild muscular hypotonia. Metabolic screening and chromosome analysis showed normal results. Molecular karyotyping revealed a *de novo* microduplication dup17p12 including the *PMP22* gene, known to be causative for Charcot-Marie-Tooth disease type 1A (CMT1A). The age of onset for motor development delay in CMT1A is around 12 +/- 7 years, suggesting a possible contribution to the child´s developmental disorder, the foot deformity as well as the hearing impairment. Since the dysmorphic features, the renal agenesis, the vision impairment and the obvious psychomotor delay could not be fully explained by a CMT1A disease, exome sequencing was performed and revealed a *de novo* pathogenic nonsense mutation c.1837C>T, p.R613*, in the *WAC* gene on chromosome 10. The diagnosis of *WAC*-related DeSanto-Shinawi syndrome matched some of the girl´s facial features such as synophrys, broad/prominent forehead, depressed nasal bridge and bulbous nasal tip. Hypotonia and unspecific vision impairment are also described in some of the few published cases with DeSanto-Shinawi syndrome. Motor development delay, hearing impairment and foot deformities are features seen in both CMT1A and DeSanto-Shinawi syndrome. We obtained informed consent from the parents of the girl for presenting her case. This report shows the importance of clinical genetics in order to initiate further investigations when a diagnosis does not fully explain a patient´s phenotype. DeSanto-Shinawi syndrome is a recently described (2015) genetic disorder, and even though many symptoms and dysmorphologies match the symptoms of most affected patients, some associations such as kidney malformations need further exploration.


a)


b)


c)

a) the girl was not able to stand on her feet by herself

a) and b) mild dysmorphic features, including broad/prominent forehead, synophrys, depressed nasal bridge and bulbous nasal tip

b) foot deformity

A case of atypical Cornelia del Lange phenotype associated with a PHIP variant and a MYH7-related cardiomyopathy

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Cornelia de Lange syndrome (CdLS) is a rare multisystem congenital developmental disorder syndrome characterized by distinctive facial anomalies, short stature, developmental delay, hirsutism, gastrointestinal abnormalities and upper limb reduction defects. Craniofacial features include synophrys, arched eyebrows, long eyelashes, small widely-spaced teeth and microcephaly. Beside classic CdLS phenotype, other overlapping phenotypes (Cornelia-like phenotypes) have been defined by the scores outlined by the last international consensus statement.
CdLS syndrome has been classically associated with cohesin complex coding genes like SMC1A, SMC3, RAD21.
We report a Cornelia-like phenotype in a 3-year-old boy also affected by a MIHY7-related cardiopathy. At birth the boy presented oesophageal atresia with fistula, horseshoe kidneys, cardiomyopathy, cerebral malformation, hirsutism and minor facial dysmorphism. The patient shows a global developmental delay and postnatal growth retardation. He presents 10 points in CDLs clinical score, consistent with a non-classical CdLs phenotype. Whole exome sequencing analysis identified the presence of two heterozygous variants in MYH7 associated with familial hypertrophic cardiomyopathy - and in PHIP. The same variants in MYH7 and PHIP were then identified in his mother, who presents a milder but partially overlapping phenotype (CdLs clinical score 8). Also, his maternal grandfather was then diagnosed with a MYH7-related cardiopathy while the PHIP variant was not identified in his grandparents.
The variant identified in PHIP has never been described and is classified as probably pathogenetic. In literature only another variant in PHIP has been described as associated with Cornelia-like phenotype. The same study described different CdLs and Cornelia-like phenotypes associated with other variants in different genes never associated to CDLS before and not strictly related with the cohesin complex. Further studies to support this correlation are needed, however we believe that this case is an example of how the synergy between the use of clinical criteria and the use of WES analysis can lead to an early diagnosis together with an expansion of knowledge on etiopathogenesis and on the genes responsible for complex syndromes.

Schwartz-Jampel syndrome: three sisters with an additional cardiac phenotype

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Schwartz-Jampel syndrome (#255800), also called chondrodystrophic myotonia, is a rare autosomal recessive condition caused by *loss of function* mutations in the *HSPG2* gene. The syndrome is characterized by growth retardation, osteochondrodysplasia, clinical myotonia, joint contractures, muscle hypertrophy and a characteristic "mask-like" face. Typical facial features consist of blepharophimosis, narrow palpebral fissures, low-set ears, micrognathia, microstomia and pursed lips. The facial appearance becomes more characteristic with age.
Here we describe three sisters with Schwartz-Jampel syndrome with a previously undescribed additional cardiac phenotype.
All three sisters, 10, 9 and 6 years old, presented with the typical clinical features of Schwartz-Jampel syndrome: short stature (3/3), enlarged knees (3/3), microstomia (3/3), micrognathia (3/3), deep set ears (3/3), deep frontal hairline (3/3), narrow and upslanting palpebral fissures (2/3), blepharophimosis (2/3) and puckered chin (2/3). In all three sisters a non-compaction cardiomyopathy was diagnosed in addition, which was not previously published in Schwartz-Jampel syndrome. Whole-exome sequencing revealed a homozygous likely pathogenic missense variant in the *HSPG2* gene (NM_005529.7:c.5273G>A p.(Arg1758Gln)) in all three sisters. This *HSPG2* variant has not been reported so far in GnomAD (v2.1 and 3.1). Segregation analysis confirmed a heterozygous carrier status of the consanguineous parents.
We further identified a homozygous missense variant of unknown significance in *TRIM63* (NM_032588.4:c.224G>A p.Cys75Tyr) in all three sisters. *TRIM63* is localized in the same loss-of-heterozygosity region as *HSPG2,* which is present in the three sisters. Mutations in the *TRIM63* gene have previously been reported as candidates for the development of cardiomyopathies. A recent paper by Salazar-Mendiguchía et al. (2020) reported on rare homozygous or compound heterozygous variants in *TRIM63* in 16 patients with an autosomal recessive form of cardiomyopathy, however most patients displayed hypertrophic cardiomyopathy and the mean age of onset were 35 years (range 15-69).
We will further delineate the clinical spectrum of Schwartz-Jampel syndrome and discuss the genetic basis of the cardiomyopathy observed in the three sisters.

A case of overlapping NOONAN and MARFAN syndromes

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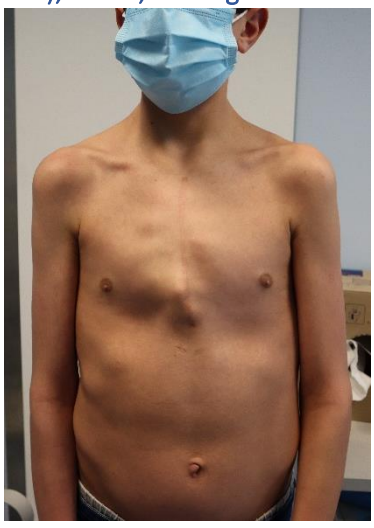
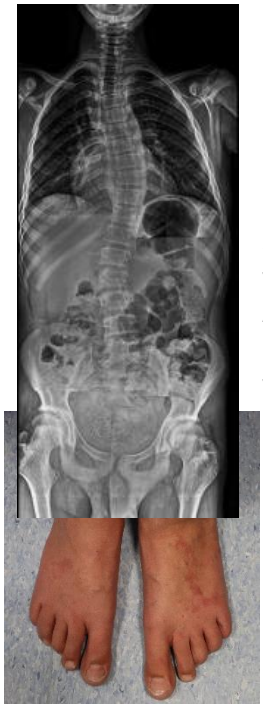
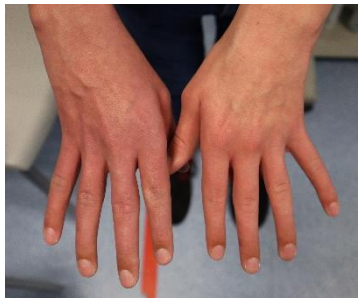


We report a 15-year-old male patient, born to non-consanguineous parents and with congenital anomalies of the heart, ventricular hypertrophy and CAKUT.
His mother has Marfan syndrome (MS) (MIM#154700) with molecular confirmation of a pathogenic variant in *FBN1* gene and his younger brother (14 years old) also has clinical features of MS.
He also was confirmed to have the diagnosis of MS. The genetic test was done due to the association of his family history and clinical signs of tricuspid valve dysplasia, mitral valve prolapse and aortic annulus dilation (Z score +3) with mild aortic insufficiency. He has slender build, downslanted palpebral fissures with asymmetric ptosis, high and narrow palate, dental crowding, pectus carinatum and asymmetry of the thorax, wide intermammillary distance, arachnodactyly, adducted thumbs, genu valgum and talipes calcaneovalgus, pes planus and long halluces. Long-spine plain film showed thoracic levoscoliosis (Cobb angle of 20.4), a less prominent lumbar dextroscoliosis and bilateral *coxa valga*. Ghent systemic score for MS is 10 points and genetic testing confirmed heterozygosity for the familial variant in gene *FBN1*.



As the patient also presented features that remained unexplained by the diagnosis of MS, namely a double-chambered right ventricle, infundibular obstruction, asymmetric right ventricular hypertrophy, congenital ureteropelvic junction obstruction, scapular winging, "*café-au-lait*" spots and peripheral edema (non-pitting), and also some dysmorphic facial features. Measurements revealed stature in the lower range of normal (5-15th percentile) and normal arm span/stature ratio (1,01) with no joint hyperlaxity. A Noonan syndrome was suspected and a NGS panel of 13 genes related to RASopathies was performed, which revealed a heterozygous variant c.170C>G p.(Ala57Gly) in *RIT1* (NM_006912.5) gene. This variant is classified as pathogenic for Noonan syndrome (NS) (MIM# 615355).



According to the literature, pathogenic variants in *RIT1* are found in 5% of individuals with NS. The *RIT1* encodes a protein of the subfamily RAS and gain-of function variants in this gene result in Noonan phenotype with a greater incidence of hypertrophic cardiomyopathy and a high incidence of perinatal abnormalities, hyperpigmentation and wrinkled palms and soles, but lower prevalence of short stature or pectus deformity than in NS caused by variants in other genes.
The parents are unavailable for further study, so the patient was diagnosed with both MS and NS, and will follow surveillance accordingly.

Common dilemma in uncommon disorders: patient presenting with symptoms of two rare diseases or atypical presentation of one rare disorder.

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14-year old girl (e.g. Anna) was referred from Genetic Clinic to Pediatric Department to expand diagnostics due to suspicion of family history of Wilson's disease. Anna's Grandmother (father's mother) died due to hepatic failure, she was clinically diagnosed with Wilson's disease, awaiting for liver transplant, but there were no medical documents available to review. Anna's father left them a long time ago. Anna had ceruloplasmin level checked 9 years ago - the result was low normal (20,6 mg/dl; N 20-60)

Past medical history : Anna was born from 2nd pregnancy, 2nd labour, on term, 3800g, APGAR 10; pregnancy uneventful. Postnatally - hyperbilirubinemia (phototherapy), thrombocytopenia – no medical data available. Anna's psychomotor and speech development was within normal range. Nowadays Anna is at high school, she has no major learning difficulties, she often complaints of being tired.

Anna attends :

Allergology Clinic - since early childhood she suffered from oedematic episodes (eyelids, cheeks, sporadicaly legs), usually after eating products with preservatives. Anna suffered from recurrent respiratory tract infections, but she no immunodeficiency

Ophtalmology Clinic – bilateral myosis, difficulties in visual acuity after dark

Furthermore, she complaints of recrrent episodes of headaches, lasting for few days, resolving spontaneously or after medications, no morning/preprandial vomiting/nasuea, no visual difficulties, no signs of URTI; she wasn't consulted neurolgically so far

Otherwise Anna has a good apetite, no vomiting/nausea, no problems with passing stools/urine, no symptoms of respiratory tract infection. Vaccinations done. No constant medications.

On admission, the girl was in good general condition, vital signs : HR 85/min, RR 20/min, BP 100/60. Abnormalities on physical examination: bilateral myosis, hypotelorism, periodically marbled skin, silent heart murmur 1/6 in Levine scale, slight contracture of Achilles tendons on both sides (probably after habitual toe walking in earlier years). Weight : 47 kg (22 pc) Height : 151 cm (2 pc) BMI 20.6 (61 pc)

Abnormal lab test results: increased CK (2106 U/l), hypocalcemia (Ca 8.4 mg/dl).

Reduced blood copper concentration, ceruloplasmin 0.22 [G/l]

AbdoUSS: hepatomegaly with fibrosis, the spleen was not visualized.

AbdoMRI: No spleen. Larger liver, no focal changes, normal echogenicity.

Head MRI: no focal changes in the brain (only benign arachnoid cyst).

Cardiology consultation: aortic regurgitation I / IIst.

In neurological examination: narrow, symmetrical pupils, trace reaction to light? No signs of neurological focal injuries.

Ophthalmological consultation: no Kaiser-Fleisch ring

The Stormorken syndrome was suspected – on molecular examination - pathogenic variant in the STIM 1 NM_001277961 gene: c.910C> T. Molecular test of Wilson's syndrome is under analysis.

The family members – mother and 2 sisters' DNA is being analyzed - there was a history of thrombocytopenia in all 3 of them.

Familial thymoma in twins with Koolen-De Vries Syndrome (E Pisan)

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Koolen-de Vries syndrome is a dysmorphic syndrome associated with neurodevelopmental disorder caused by haplo-insufficiency of *KANSL1*, which plays a role in transcription regulation. This syndrome is not known to be associated with tumor. We report here monozygotic twins with Koolen-de Vries syndrome who both developed thymoma. Diagnosis was made by Whole Exome Sequencing (WES). No other variant explaining thymoma was found. To our knowledge no etiology of familial thymoma has been found yet. Occurrence of thymoma at the same age in monozygotic twins strongly suggests a genetic predisposition.

Whole exome sequencing is the minimal technological approach in probands born to consanguineous couples

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5 Translational Cytogenomics Research Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy.
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We report on two siblings suffering from different pathogenic conditions, born to consanguineous parents. A multigene panel for brain malformations and microcephaly identified the homozygous splicing variant NM_005886.3:c.1416+1del in the KATNB1 gene in the older sister. On the other hand, exome sequencing revealed the homozygous frameshift variant NM_005245.4:c.9729del in the FAT1 gene in the younger sister, who had a more complex phenotype: besides bilateral anophthalmia and heart defects, she showed right split foot with 4 toes, 5 metacarpals, 2nd toe duplication and preaxial polydactyly on the right hand. These features have been never reported before in patients with pathogenic FAT1 variants and support the role of this gene in the development of limb buds. Notably, each parent was heterozygous for both of these variants, which were ultra-rare and rare, respectively. This study raises awareness about the value of using whole exome/genome sequencing rather than targeted gene panels when testing affected offspring born to consanguineous couples. In this way, exomic data from the parents are also made available for carrier screening, to identify heterozygous pathogenetic and likely pathogenetic variants in genes responsible for other recessive conditions, which may pose a risk for subsequent pregnancies.

Session 12: Syndrome delineation single cases

Two cases of Pitt – Hopkins syndrome

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Pitt-Hopkins syndrome (PTHS, MIM#610954; ORPHA: 2896) is defined by severe psychomotor delay, epilepsy, diurnal hyperventilation episodes and distinctive facial features. PTHS is caused by haploinsufficiency of TCF4 resulting from either a pathogenic variant in TCF4 or a deletion of the chromosome region 18q21.2 where TCF4 is located. Most individuals reported to date have a de novo pathogenic variant or deletion. Here we report two unrelated Lithuanian girls (now aged 16 and 15) with PTHS phenotype: a narrow forehead, strabismus, a large nose with low hanging columella, full cheeks, wide mouth and thickened helices, slender fingers, unstable gait, severe intellectual disability with absent speech. Clinical heterogeneity of PTHS made it difficult to identify the diagnosis due to the phenotype overlap with other syndromes. De novo pathogenic variant c.1739G>A (p.(Arg580Gln)) and a variant of unknown significance c.1877G>A (p.(Arg626Gln)) in TCF4 gene were detected by whole-exome sequencing (WES), revealing the diagnosis of PTHS for these patients. Recent studies suggest that TCF4 pathogenic variants are involved in pathogenesis of amount of unsolved cases of nonsyndromic intellectual disability. However the successful recognition of dysmorphic features and exome sequencing can facilitate the diagnosis at early age efficiently detecting disease-causing genetic mutations within any gene in the human genome.

Two compound heterozygous novel missense variants in *SPART* cause mitochondrial dysfunction and cell cycle arrest associated with Troyer Syndrome

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Bi-allelic pathogenic variants in *SPART* (OMIM *607111) have been associated with Troyer syndrome (OMIM #275900), a form of spastic paraplegia presenting with lower extremity spasticity and weakness, degeneration of corticospinal tract axons, short stature and cognitive defects.
SPART encodes for Spartin, a multifunctional protein consisting of an N-terminal domain, interacting with microtubules for protein trafficking, and a C-terminal senescence domain. Previously it has been found that homozygous loss-of-function variants in *SPART* cause mitochondrial dysfunction characterized by Complex I impairment and altered pyruvate metabolism.
Here we present a 6-year-old boy with short stature and muscle weakness with reduced walking distance as well as developmental delay. Performing whole-exome sequencing, we identified two novel compound heterozygous missense variants in *SPART (both class 3), one maternally and one paternally inherited.*
Functional analysis performed on the patients´ fibroblasts showed an altered mitochondrial network, decreased activity of the oxidative phosphorylation system (OXPHOS) and ATP levels, increased mitochondrial reactive oxygen species (ROS) production, increased mitochondrial membrane potential and altered Ca^{2+} levels vs. control fibroblasts.
Interestingly, re-expression of *SPART* restored both the ATP/ADP ratio and intracellular Ca^{2+} levels to control levels, providing the evidence that these observed defects were specifically caused by mutated Spartin.
Immunofluorescence staining in control and patient-derived fibroblasts revealed a marked nuclear localization of Spartin in the mutant cells, whereas in controls it was evenly distributed in the cells. Noticeably, cell cycle analysis revealed that patients´ fibroblasts were retained in S phase.
In addition, decreased levels of Coenzyme Q10 (CoQ10) compared to control fibroblasts, along with the decrease COQ7 and COQ9 (two enzymes involved in the formation of Q10) was detected. Supplementing patient's fibroblasts with CoQ10 caused increased ATP synthesis compared to untreated patients´ fibroblast.
Our findings suggest CoQ10 supplementation as an interesting therapeutic approach for the patient, which should be tested *in vivo*.

A novel variant in *POGZ* in a boy with White-Sutton Syndrome

(Macedo C.[1], Soeiro e Sá M.[1], Sousa A.B.[1])

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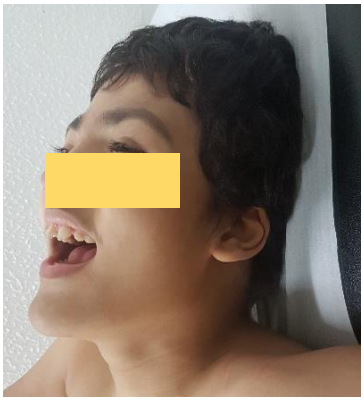
We present a 14-year-old boy with healthy nonconsanguineous parents. He has a paternal cousin with epilepsy, but no other relevant family history. He presented with severe hypotonia and feeding difficulties soon after birth and evolved with moderate to severe developmental delay (DD). At his first Genetics evaluation, aged 12, he had severe intellectual disability (ID) with absent language and no autonomous walking, autistic behaviour (no interest in the surrounding environment, manual and vocal stereotypies, and self-injurious behaviour), microcephaly, facial dysmorphisms (narrow forehead, hypertelorism, narrow palpebral fissures, wide nasal bridge, wide mouth with downturned corners, and low-set and posteriorly rotated ears), sensorineural deafness, and seizures. Meanwhile, he started to suffer from refractory severe sleep-wake cycle disturbance.



Array-CGH and *FMR1* molecular analysis were normal. Whole Exome Sequencing (WES) identified a novel heterozygous *POGZ* truncating variant, classified as likely pathogenic. Subsequent parental studies confirmed the variant was *de novo*.

Inactivating *POGZ* pathogenic variants are associated with White-Sutton syndrome (WSS) (OMIM#616364), which is a rare, recently described, autosomal dominant syndrome, with only about 50 cases reported in the literature so far. *POGZ* encodes a multidomain nuclear protein involved in transcriptional regulation. WSS is characterized by mild to severe DD/ID, neonatal hypotonia, autism spectrum disorder (ASD), facial dysmorphisms, hearing and visual impairment, and epilepsy. Although a few patients have been reported to have sleep disturbances, this case seems to represent a particularly severe presentation of this feature. Despite several pharmacological trials, our patient maintains severe and cumulative sleep deprivation. According to his parents, he has spent a maximum of five consecutive days without deep sleep.

Given the wide range of clinical manifestations of WSS, our case highlights the emergent role of the genotype-first approach in the New Generation Sequencing (NGS) era of Clinical Genetics. More research and publications are needed to better define the phenotype of WSS, allowing an earlier diagnosis and the development of personalized approaches and follow-up strategies for these patients and their families.

Figure 1 - Facial characteristics of our patient showing microcephaly, narrow forehead, hypertelorism, bilateral epicanthus, short and narrow palpebral fissures, wide nasal bridge, short philtrum, wide mouth with downturned corners, full lips and low-set and posteriorly rotated ears.

Expanding the genotypic and phenotypic spectrum of a rare HGPPS2 syndrome

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Horizontal Gaze Palsy with Progressive Scoliosis-2 with impaired Development (HGPPS2) is a rare congenital disorder characterized by absence of conjugate horizontal eye movements, progressive scoliosis developing in childhood, developmental delay, agenesis of corpus callosum and absence of cerebral commissures.

The deleted in colorectal cancer (*DCC*) gene encodes the netrin-1 (NTN1) receptor DCC, a transmembrane protein required for the guidance of commissural axons. Pathogenic germline *DCC* variants disrupt the development in the central nervous system. Monoallelic, pathogenic missense, and predicted loss-of function *DCC* variants cause congenital mirror movements, isolated agenesis of corpus callosum or both. Biallelic, predicted loss-of-function DCC variants cause developmental split-brain syndrome (DSBS) also called as HGPPS2 (MIM #617542).

We report here on the phenotype of a 9-year-old girl of consanguineous parents from Syria. She is the youngest of three siblings. She was born at term from an uneventful pregnancy by Cesarean section. She has had significant failure to thrive and her development has been markably delayed. She learned to walk at the age of 8 years old. She can not speak. She was diagnosed with severe intellectual disability after moving to Finland at the age of 8years old. She is small, her height is -4.5SD. Her head MRI showed complex abnormalities in the midline including agenesis of corpus callosum. In addition, mesencephalon and pons are abnormal. She has progressive scoliosis and her eyes moves only vertically, not horizontally.
Exome sequencing revealed a biallelic (homozygous) duplication within the *DCC* gene; she has four copies of exons 13-15. Both parents are carriers of this small tandem duplication. c.1912_2359dup. p.(Ser788Tyrfs*4) confirming the recessive segregation. Since this type of variant has not been described earlier, it is in ACMG category 3 (VUS). We speculate that this homozygous duplication will break the reading frame and causes a preterm stop codon and due to loss-of-function causes the phenotype in our patient.
To date only handful of patients have been described with mutations in this *DCC* gene. Our findings expand the genotypic and the phenotypic spectrum of the rare HGPPS2 syndrome caused by pathogenic biallelic variants in the *DCC* gene. We have demonstrative videos of her ophthalmological testing. Securing a diagnosis provides crucial information to the family for recurrence risk.

A case of lissencephaly due to a variation in the *CEP85L* gene: case report, clinical and molecular aspects

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Lissencephaly describes a group of conditions characterized by the absence of normal cerebral convolutions and abnormalities of cortical development. To date, at least 20 genes have been identified as involved in the pathogenesis of this condition. Variants in *CEP85L*, encoding a protein involved in the regulation of neuronal migration, have been recently described as causative of lissencephaly with a posterior-prevalent involvement of the cerebral cortex and an autosomal dominant pattern of inheritance. Here we describe a 3-year-old boy with slightly delayed psychomotor development and mild dysmorphic features including bitemporal narrowing, protruding ears with up-lifted lobes and posterior plagiocephaly. Brain MRI at birth identified type 1 lissencephaly, prevalently in the temporo-occipito-parietal regions of both hemispheres with "double-cortex"

(Dobyns' 1-2 degree) periventricular band alterations. Whole-exome sequencing revealed a previously unreported, *de novo* pathogenic variant in the *CEP85L* gene (NM_206921:c.232+1del). Only 20 patients have been reported as carriers of pathogenic *CEP85L* variants to date. They show lissencephaly with prevalent posterior involvement, variable cognitive deficits and epilepsy. Comparing the phenotypic and molecular findings with those of other known cases, it underlines the importance of carefully evaluating the EEG pattern, the possible presence of other anatomical anomalies (such as any dysmorphism of the corpus callosum or partial hippocampal malrotation) and the concomitant presence of SBH. Neurodevelopment can have a favorable evolution despite the presence of relevant MRI findings. Our findings and the other scientific report suggest the possible presence of a hot-spot region of pathogenic variants located at the donor splice site of exon 2 and within exons 1 and 2.

Session 13: Syndrome delineation single cases

The phenotypic spectrum of BRAT1-related disorders: 51 additionnal cases and litterature review

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BRAT1 bi-allelic mutations have been associated with two distinct clinical pictures: the rigidity and multifocal seizure syndrome (RMFSL) and a neurodevelopmental disorder associating cerebellar atrophy with or without seizures syndrome (NEDCAS). To our knowledge, 37 patients from 26 families have already been described with recessive variations in *BRAT1*. We report here clinical and molecular findings of 51 patients from 39 families

with bi-allelic pathogenic variants in the BRAT1 gene. Prenatal features were observed in 3 patients (3/39; 8%). Microcephaly was observed in 22 of 41 patients (54%) and was already present at birth in 6 of 45 patients (13%). Hypotonia was noted in 28 of 44 patients (64%) and hypertonia of the limbs in 23 patients (46%). Intellectual disability was noted in all patients, except one. All but this one showed developmental delay, without any psychomotor acquisition for 41% of them (21/51). Only 48% of patients (24/50) acquired walking. Ataxia was present in 41% of cases (21/51). Epilepsy was present in 51% of patients (26/51). Mean age of onset was around one year of life (358 days) ranging from in utero to 13 years old. First seizures occurred before the age of one year in 81% of cases (21/26), and in 50% of cases (13/26) in the first week of life. In the majority of cases, epilepsy was drug resistant (20/26 ; 77%). Brain MRI showed cerebral atrophy in 13 patients (13/49; 27%) and cerebellar atrophy in 34 patients (34/49; 69%). Death occurred in 18 patients (35%), before the age of 1 year for 14 of them (28%). The phenotype of our patients seems less severe than that described in the literature. This might be explained by the difference in the representation of truncating and missense mutations. We therefore suggest that biallelic *BRAT1* variants are not associated with two distinct clinical presentations but rather with a broader phenotypic spectrum. The most severe end of this disorder, mainly seen in patients with two truncating variations, is associated with profound intellectual disability, drug-resistant epilepsy, cerebral atrophy and early death. At the other end of the spectrum, a phenotype of mild ID, cerebellar atrophy, ataxia, nystagmus and higher life expectancy is observed in patients with at least one missense variant.

A distinctive primordial dwarfism syndrome caused by PRIM1 deficiency

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DNA replication is fundamental for cell proliferation in all organisms. Components of the replisome have been implicated in human disease. Our group reported PRIM1 encoding the catalytic subunit of DNA primase as a novel disease gene in 2020 (PMID 33060134). Using a variant classification agnostic approach, biallelic mutations in PRIM1 were identified in five individuals, and one additional since the publication of our paper, from four unrelated families. All patients showed severe primordial dwarfism and distinctive facies with broad, prominent forehead, small palbepral fissures, microtia, horizontal mouth, feeding problems, failure to thrive and decreased subcutaneous fat tissue. All except one patient died before two years of age due to B-cell aplasia

and consequent infections. Chronic parenchymal lung disease, pulmonary hypertension and in three patients, hepatic fibrosis were detected, reflecting a persisting inflammatory state.
Homozygous intronic variant in the PRIM1 gene resulting in the activation of a cryptic donor site and disruption of the open reading frame was detected in four individuals. In one patient, compound heterozygous mutations including an essential splice donor variant and a missense variant were identified.
PRIM1 protein levels were markedly reduced and fork defects were seen in patient cells. Cell proliferation was markedly impaired, explaining the patients' extreme growth failure. Notably, phenotypic features distinct from those previously reported with DNA polymerase genes were evident.

De novo variants in MED12 cause X-linked syndromic neurodevelopmental disorders in females

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MED12 is a subunit of the Mediator multiprotein complex with a central role in RNA polymerase II transcription and regulation of cell growth, development and differentiation. Missense variants in *MED12* are causative for variable X-linked recessive phenotypes including Ohdo-, Lujan-, and FG syndromes.

By international matchmaking we assembled data on 18 females with *de novo* variants in *MED12* and variable neurodevelopmental disorders. Five nonsense variants clustered in the C-terminal region, two splice variants were found in the same exon 8 splice acceptor site, and 11 missense variants were distributed over the gene/protein. Protein truncating variants were associated with a severe, syndromic phenotype consisting of intellectual disability (ID), facial dysmorphism, short stature, skeletal abnormalities, feeding difficulties and variable other abnormalities. De novo missense variants were associated with a less specific, but homogeneous phenotype including severe ID, autistic features, limited speech and variable other anomalies, overlapping both with females with truncating variants as well as males with missense variants.
We establish *de novo* truncating variants in *MED12* as causative for a distinct NDD and *de novo* missense variants as causative for a severe, less specific NDD in females.

Further characterization of female Borjeson-Forssman-Lehmann syndrome caused by *de novo* variants in *PHF6*

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While inherited variants in *PHF6* cause X-linked recessive Borjeson-Forssman-Lehmann syndrome (BFLS) in males, *de novo* variants were reported in 14 females, so far, associated with an overlapping but distinct phenotype. They present with moderate to severe intellectual disability, a characteristic facial gestalt, teeth anomalies, finger and toe anomalies and linear skin pigmentation. We now assembled data on eight additional female individuals with *de novo* variants in *PHF6* and the typical female BFLS phenotype, thus further defining the clinical spectrum. The mutational spectrum comprises an intragenic deletion, four truncating variants and three missense variants located in the PHD2 domain and predicted to severely affect protein structure stability. This observation supports the hypothesis of more severe variants in females contributing to genotype-phenotype correlations between genders.
Our findings therefore further delineate the clinical and mutational spectrum of female BFLS and provide further insights into possible genotype-phenotype correlations between females and males.

RNU4ATAC biallelic mutations: from Roifman syndrome to microcephalic osteodysplastic primordial dwarfism, type I (MOPD1). Description of four new patients

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Introduction: *RNU4ATAC* homozygous and compound heterozygous variants were recently reported to cause MOPD1 (OMIM 210710) and Roifman syndrome (OMIM 300258). Our work expands the phenotypic spectrum of patients with *RNU4ATAC* mutations.
Material and Methods: Here we report four further patients from three unrelated families with biallelic variants in *RNU4ATAC*. Three patients had clinical diagnosis of Roifman syndrome and one of MOPD1. In patient 1 the diagnosis was uncovered by genome sequencing, in siblings from family 2 and patient 4 by direct Sanger sequencing because of clinical suspicion.
Results: Main clinical characteristics of our patients with Roifman syndrome include skeletal dysplasia (3/3) with short stature (3/3), intellectual disability (3/3), antibody deficiency (3/3) and retinal dystrophy (2/3). Dysmorphic features shared by the three patients were markedly long philtrum and thin upper lip. Hepatomegaly was identified in 2/4 and patient 1 presented hepatic cavernoma (previously unreported). Patient 4, with the MOPD1 phenotype, presented severe short stature and microcephaly with poorly developed gyri and agenesis of corpus callosum. Dysmorphic features included sparse hair, absent eyebrows, prominent eyes and nose. Skeletal changes and eye pigmentation in this patient was also different from the epiphyseal dysplasia and retinal dysplasia typical of Roifman Syndrome. Finally, no evidence of primary immunodeficiency was detected in MOPD1 patient.
Genome sequencing in patient 1 identified n. 8C>T and n.50 G>A variants. Sanger sequencing of *RNU4ATAC* in siblings patient 2 and 3 identified n.13C>T and n.17 G>C variants whereas in patient 4, n.51G>A variant was identified in homozygous state. Each variant was inherited from respective healthy parents in the three families.

Conclusions: The description of new patients with biallelic *RNU4ATAC* variants is essential to further delineate the phenotype of this allelic spectrum. The recognition of the phenotype in both entities is indispensable for the orientation of molecular diagnosis.
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PHIP-associated Chung-Jansen syndrome: report of four new individuals

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In 2018, Jansen and colleagues described a new syndrome mainly characterized by developmental delay (DD), learning difficulties/intellectual disability (ID), behavioral abnormalities, facial dysmorphism and obesity due to haploinsufficiency of *PHIP* (pleckstrin homology domain interacting protein, OMIM *612870, CHUJANS, #617991). As only ~35 patients have been published so far, it appears to be a rare cause of DD/ID.
We report four additional individuals with newly identified *PHIP* variants (two probably pathogenic missense variants, detected by whole exome sequencing, as well as two deletions detected by array analysis, both partially effecting the *PHIP* gene). One deletion of 57 kb in size is localized within the *PHIP* gene and affects exons 5-15. The other deletion, 1.68 – 1.72 Mb in size, also results in a partial deletion of the *PHIP* gene and also removes six adjacent genes/loci. Confirmation testing and segregation analysis of the two sequence variants by Sanger sequencing showed *de novo* occurrence. Quantitative PCR analysis / array analysis of the deletions in the parents revealed that both were inherited from a (mildly) affected parent. In accordance with the previously described patients, all four individuals reported here show developmental delay, learning disability or ID, behavioral abnormalities, weight problems with increasing age and characteristic craniofacial features (prominent eyebrows, thick alae nasi, and long philtrum).
Our findings further expand the mutational spectrum of *PHIP.* We discuss the molecular and clinical features in comparison to the published individuals.

Session 14: Epi-signatures

Heterozygous variants in KDM2B cause a neurodevelopmental syndrome with variable congenital anomalies and a specific dna methylation signature

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Introduction: Lysine-specific demethylase 2B (KDM2B) is a histone demethylase implicated in chromatin modification and regulation of gene expression. It shows strong constraint against loss-of-function variants and

additionally the DNA-binding CXXC-domain is highly intolerant of missense variation. KDM2B binds to non-methylated CpG islands through this domain, to act as a transcriptional repressor. Loss of KDM2B leads to DNA hypermethylation in mouse models and KDM2B-deficient mice show early embryonic lethality with severe congenital malformations and growth restriction.
Methods and results: Through exome sequencing and international data sharing, we identified 14 heterozygous *KDM2B* variants in 17 patients. The patients have a variable degree of developmental delay and/or intellectual disability. Additional features include autism, ADHD and cardiac, renal and ophthalmological defects. The variants occurred mostly *de novo* but were inherited from a mildly affected parent in two families. We found three truncating variants and a deletion of *KDM2B,* plus ten missense variants, eight of which cluster in the CXXC-domain. Methylation analysis on leucocyte-derived DNA showed a shift towards hypermethylation in patients with pathogenic variants, parallel to the KDM2B- depleted mouse models. These findings suggest a loss-of-function mechanism. We were able to detect a specific *KDM2B*-associated DNA methylation signature. Interestingly, we were able to detect this signature in two patients in our cohort with a second genetic diagnosis. Additionally, the signature was present in three patients from a previously reported SETD1B cohort with a microdeletion including both KDM2B and SETD1B.
Conclusion: Heterozygous pathogenic variants in *KDM2B* cause a neurodevelopmental syndrome with variable congenital anomalies and a specific methylation signature.

SPEN haploinsufficiency causes a neurodevelopmental disorder overlapping proximal 1p36 deletion syndrome with an episignature of X chromosomes in females

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Deletion 1p36 (del1p36) syndrome is the most common human disorder resulting from a terminal autosomal deletion. This condition is molecularly and clinically heterogeneous. Deletions involving two non-overlapping regions (*i.e.,* distal and proximal critical regions), are sufficient to cause the majority of the recurrent clinical features, although with different facial features. *SPEN* encodes a transcriptional repressor commonly deleted in proximal del1p36 syndrome and is located centromeric to the proximal 1p36 critical region. Here, we used clinical data from 34 individuals with truncating variants in *SPEN* to define a novel NDD that overlap considerably with the proximal del1p36 syndrome.
The clinical profile of this disease includes DD/ID, autism spectrum disorder, anxiety, aggressive behavior, attention deficit disorder, hypotonia, brain and spine anomalies, congenital heart defects, high/narrow palate, facial dysmorphisms, and obesity/increased BMI, especially in females. *SPEN* also emerges as a relevant gene for del1p36 syndrome by co-expression analyses. Finally, haploinsufficiency of SPEN is associated with a distinctive DNA methylation episignature of the X chromosome in affected females, providing further evidence of its crucial role in the epigenetic control of this chromosome, and a paradigm of an X chromosome-specific episignature that classifies syndromic traits. We conclude that SPEN haploinsufficiency is a major contributor to a disorder associated with deletions centromeric to the previously established 1p36 critical regions.

Loss-of-function and missense variants in *NSD2* cause decreased methylation activity and are associated with a distinct developmental phenotype ***(2021 Best presentation)***

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PURPOSE: Despite a few recent reports of patients harboring truncating variants in *NSD2*, a gene considered critical for the Wolf–Hirschhorn syndrome (WHS) phenotype, the clinical spectrum associated with *NSD2* pathogenic variants remains poorly understood.
METHODS: We collected a comprehensive series of 18 unpublished patients carrying heterozygous missense, elongating, or truncating *NSD2* variants; compared their clinical data to the typical WHS phenotype after pooling them with ten previously described patients; and assessed the underlying molecular mechanism by structural modeling and measuring methylation activity in vitro.
RESULTS: The core *NSD2*-associated phenotype includes mostly mild developmental delay, prenatal-onset growth retardation, low body mass index, and characteristic facial features distinct from WHS. Patients carrying missense variants were significantly taller and had more frequent behavioral/psychological issues compared with those harboring truncating variants. Structural in silico modeling suggested interference with NSD2's folding and function for all missense variants in known structures. In vitro testing showed reduced methylation activity and failure to reconstitute H3K36me2 in *NSD2* knockout cells for most missense variants.
CONCLUSION: *NSD2* loss-of-function variants lead to a distinct, rather mild phenotype partially overlapping with WHS. To avoid confusion for patients, *NSD2* deficiency may be named Rauch–Steindl syndrome after the delineators of this phenotype.

Episignature analysis in 4 patients broadens the clinical spectrum of ATRX syndrome

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X-linked alpha thalassaemia mental retardation (ATRX) syndrome (OMIM #301040), described in early nineties, was initially associated with profound developmental delay, particular facial appearance, alpha-thalssemia trait and genital abnormalities (Gibbons et al. 1995). Subsequent descriptions have shown that alpha thalassaemia is not a mandatory feature and ID can be moderate. This syndrome is caused by pathogenic variants in the *ATRX* gene, located on X chromosome and encoding the ATRX protein, a member of the Snf2 family of chromatin-remodelling proteins. The molecular mechanisms underlying the ATRX syndrome are not completely understood. However, it has been demonstrated that *ATRX* pathogenic variants cause changes in the pattern of genomic DNA methylation. Recently, Sadikovic's team showed that ATRX syndrome has a unique episignature (Schenkel et al. 2017). We used this novel approach to resolve the diagnostic uncertainty in families in desperate need of genetic counseling, which was especially critical in the context of the X-linked mode of inheritance for ATRX syndrome. We present 7 male patients from 4 unrelated families, followed for a long period of time in our center, in whom targeted genetic analyses identified 4 novel missense variants in the *ATRX* gene by targeted sequencing. Reverse phenotyping and expert multidisciplinary team meetings did not allow to confirm the diagnosis. Since patients did not harbor all characteristic features of ATRX syndrome, the identified variants were classified as being of uncertain significance (VUS). Recently, patients' sisters were referred for their genetic counselling. We clinically reviewed the probands and completed the initial targeted sequencing of *ATRX* by an extended ID gene panel sequencing and methylation analysis. Episignature supported the diagnosis of ATRX syndrome in 3 families, whereas it was excluded in the fourth, in which we identified another diagnosis. This work provides examples of the use of episignature in medical practice and highlights its utility in patients with a milder ATRX clinical presentation. Finally, we provide some elements of natural history (long term follow-up clinical data) and contribute to broadening the clinical spectrum of ATRX syndrome.

Session 15: Short reports

Unknown case with complex heart, neurological and skeletal pathology

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We present a boy, 7 years of age, born from 2nd pregnancy and 2nd delivery to unrelated parents. Pedigree was uninformative. At 26th week of gestation left heart hypoplasia was suspected. Boy was carried to term, delivered naturally, birth weight was 3940 g, length – 55 cm, head circumference – 35 cm, Apgar score – 9/9. Immediately after birth complex heart anomaly was confirmed including left heart hypoplasia, atresia of mitral and aortic valves, hypoplasia of ascending aorta, secondary atrial septal defect, open arterial duct. Several heart surgeries and a successful heart transplantation were performed. Patient also had ventriculomegaly and hydrocephaly, treated with ventriculostomy and subcutaneous reservoir. Cryptogenic focal epilepsy was diagnosed. Currently boy suffers from progressive severe hyperlordosis, hip contractures, and valgus deformity of feet. No other internal pathology was detected. Psychomotor development is delayed. Phenotype characteristics are aggravated gait and abnormal posture, general muscle hypotrophy, elbow and knee hyperextension, prominent eyebrow arches, synophrys, long eyelashes.
GAG electrophoresis was normal. SNP-CGH analysis found no pathology. Exome sequencing was performed. No pathogenic variants concordant with patient's clinical features were indentified. One heterozygous missense variant c.10616G>A, p. (Arg3539His) (rs143987857) in the *RYR1* gene of uncertain significance was found. After segregation analysis same variant was detected in healthy mother.

Vanishing bones, muscle weakness, primary microcephaly and short stature with normal cognitive development in a 4-year-old girl with consanguineous turkish parents

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Currently 4 2/12-year-old girl with unclear syndrome and progressive disease course with the following key features:

- **Growth:** IUGR, primary microcephaly, short stature
- **Muscular:** Severe hypotonia, respiratory insufficiency, muscle weakness predominantly proximal
- **Skeletal:** thinning of diaphyses, recurrent non-healing fractures, hypoplastic thorax, bilateral hip dislocation, osteolysis of clavicula
- **Renal:** large, atypically shaped kidneys and moderate chronic kidney failure
- **Endocrine:** Increased 25-OH vitamin D, GH and IGF1 deficiency, transient hyperprolactinemia and hypothyroidism
- **Ectodermal:** sparse hair, progressive frontal balding, brownish skin, dysplastic nails, multiple efflorescences
- **Ophthalmological:** hyperopia, astigmatism, strabism
- **Development:** delayed motor development, normal language and cognition
- cMRI normal, metabolic screen normal, ENMG normal

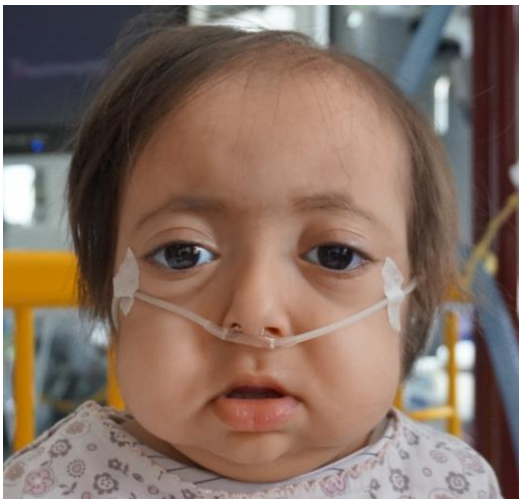

Fig. 1: patient at 2 1/12 years old

Family history: consanguineous parents from Turkey, healthy siblings
Genetic analyses:

- MLPA for *SMN1/SMN2* normal
- Array with 217 kb duplication 20p12.1 including *TASP1*, *ESF1*
- Trio exome sequencing without (likely) pathogenic variants. Several rare variants.

ANNEXES

PRESENTATION TITLE	FIRST AUTHOR	EMAIL CONTACT	#Talk
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A novel homozygous variant in GJA1 causing a Hallermann-Streiff/oculodentodigital dysplasia overlapping phenotype: a clinical report	Agnès BLOCH-ZUPAN	agnes.bloch-zupan@unistra.fr	**3**
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Two compound heterozygous novel missense variants in spart cause mitochondrial dysfunction and cell cycle arrest associated with troyer syndrome	Antje KAMPMEIER	Antje.Kampmeier@uk-essen.de	**64**
A novel variant in POGZ in a boy with white-sutton syndrome	Catarina Isabel TORRÃO	catarina.macedo@chln.min-saude.pt	**65**
Expanding the genotypic and phenotypic spectrum of a rare HGPPS2 syndrome	Maria K HAANPAA	maria.haanpaa@tyks.fi	**66**
A case of Lissencepha+A41:A64LY due to a variation in the CEP85L gene: case report, clinical and molecular aspects	Gianluca CONTRO	contro.gianluca@gmail.com	**67**
The phenotypic spectrum of BRAT1-related disorders : 51 additionnal cases and litterature review	Camille J. ENGEL	cengel@chu-besancon.fr	**68**
A distinctive primordial dwarfism syndrome caused by PRIM1 deficiency	Katalin SZAKSZON	szakszon.katalin@med.unideb.hu	**69**
De novo variants in MED12 cause x-linked syndromic neurodevelopmental disorders in females	Daniel L. POLLA	christiane.zweier@insel.ch	**70**
further characterization of female borjeson-forssman-lehmann syndrome caused by de novo variants in phf6	Céline GERBER	celine.gerber@insel.ch	**71**
RNU4ATAC biallelic mutations: from Roifman syndrome to microcephalic osteodysplastic primordial dwarfism, type I (MOPD1).	Irene VALENZUELA	mvalenzuela@vhebron.net	**72**

description of four new patients			
PHIP-associated Chung-Jansen syndrome: report of four new individuals	Alma KUECHLER	alma.kuechler@uni-due.de	**73**
Heterozygous variants in KDM2B cause a neurodevelopmental syndrome with variable congenital anomalies and a specific DNA methylation signature	Marie-Claire CORNIPS	m.c.a.cornips-2@umcutrecht.nl	**74**
SPEN haploinsufficiency causes a neurodevelopmental disorder overlapping proximal 1p36 deletion syndrome with an episignature of X chromosomes in females	F. Clementina RADIO	fclementina.radio@opbg.net	**75**
Loss-of-function and missense variants in NSD2 cause decreased methylation activity and are associated with a distinct developmental phenotype: (*2021 Best presentation*)	Paolo ZANONI	paolo.zanoni@uzh.ch	**76**
Episignature analysis in 4 patients broadens the clinical spectrum of ATRX syndrome	Alexandre ASTIER	alexandre.astier@ap-hm.fr	**77**
Unknown case with complex heart, neurological and skeletal pathology	Kamilė ŠIAURYTĖ	kamile.siauryte@santa.lt	**78**
Unsolved case	Milena STOYANOVA	genetikavarna@gmail.com	**79**

Vanishing bones, muscle weakness, primary microcephaly and short stature with normal cognitive development in a 4-year-old girl with consanguineous Turkish parents	Anaïs BEGEMANN	steindl@medgen.uzh.ch	**80**

Thursday, September 23th	Time Slot	Session Title	Expert Name	Email contact
	8:45 – 10:30 AM	New Genes	Alain Verloes	alain.verloes@aphp.fr
	11:45 AM – 1:00 PM	Syndrome delineation single cases	Dagmar Wieczorek	dagmar.wieczorek@uni-duesseldorf.de
	2:00 – 3:30 PM	Syndrome delineation single cases	Emilia K. Bijlsma	E.K.Bijlsma@lumc.nl
	4:45 – 5:45 PM	Syndrome delineation single cases	Livia Garavelli	Livia.Garavelli@ausl.re.it
	5:55 – 6:50 PM	Short reports	Isabelle Maystadt	isabelle.maystadt@ipg.be

Friday, September 24th	Time Slot	Session Title	Expert Name	Email contact
	8:45 – 10:30 AM	Tools in syndrome diagnosis	Anita Rauch	anita.rauch@medgen.uzh.ch
	11:45 AM – 1:00 PM	Syndrome delineation single cases	Connie Stumpel	c.stumpel@mumc.nl
	2:00 – 3:30 PM	Miscellaneous	Annick Toutain	annick.toutain@univ-tours.fr
	4:45 – 5:45 PM	Rasopathies	Hilde van Esch	hilde.vanesch@uzleuven.be
	5:55 – 6:50 PM	Short reports	Didier Lacombe	didier.lacombe@chu-bordeaux.fr

Saturday, September 25th	Time Slot	Session Title	Expert Name	Email contact
	8:45 – 10:30 AM	Dual diagnosis	Jüergen Kohlhase	jkohlha@t-online.de
	11:45 AM– 1:00 AM	Syndrome delineation single cases	Christiane Zweier	christiane.zweier@insel.ch
	2:00 – 3:30 PM	Syndrome delineation single cases	Claude Stoll	cstoll@unistra.fr
	4:45 – 5:45 PM	epi-signatures	Claude Stoll	cstoll@unistra.fr
	5:55 – 6:50 PM	Short reports	Koen Devriendt	koenraad.devriendt@uzleuven.be

THANKS

The Organising Committee warmly thanks all the presenters, expert guests, the Young Geneticists Network representatives and looks forward to seeing you at the 32nd session in 2022!

The Organizing Committee Co-Chairs:

Koen Devriendt
Claude Stoll
Alain Verloes

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