

EURODYSMORPHO 2022

32nd EUROPEAN MEETING ON DYSMORPHOLOGY

September 14-17 2022, Sant Joan de Déu Auditorium, Barcelona, Spain



Organised by the ERN-ITHACA, European Reference Network for Rare Malformation Syndromes, Intellectual and Other Neurodevelopmental Disorders

Scientific Committee: Pr. Koen Devriendt, Pr. Claude Stoll, and Pr. Alain Verloes







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DAY 1 – WEDNESDAY 14th OF SEPTEMBER

16h00 – SESSION 1: SKELETAL DYSLPLASIA (Chair: Annick Toutain)

16h15 - NEUROIMAGING AND SKELETAL FINDINGS IN KBG SYNDROME: A STUDY OF 52 PATIENTS

Presenting author: Stefano G. Caraffi

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Purpose: KBG syndrome is a congenital condition characterized by macrodontia of permanent upper central incisors, distinctive facial features, short stature, skeletal anomalies, developmental delay, brain anomalies and seizures. It is known to be caused by haploinsufficiency of the *ANKRD11* gene, but its prevalence is underestimated because phenotypic variability can make this syndrome difficult to recognize. Here we aim to better delineate the neuroimaging and skeletal findings in KBG syndrome.

Methods: In a collaborative study, through analysis of brain MRI and skeletal radiographs, we delineated a neuroimaging and skeletal phenotype in 52 patients with molecularly confirmed diagnosis and compared it with the features reported in the literature.

Results: The most common malformations in our cohort were enlarged cisterna magna (58%), also frequent in the literature, and hippocampal malrotation (58%), rarely reported before. Less common features were ventriculomegaly, encephalic cysts, anterior pituitary hypolasia, abnormalities of the vasculature, and patulous internal auditory canal. The most notable skeletal anomalies, apart from macrodontia and short stature, were scoliosis, vertebral abnormalities (fusion, dysmorphic bodies) including coccygeal anomalies, cervical ribs, brachydactyly (including type A4), and carpal anomalies. Skeletal maturation analysis showed a distinctive difference in the ossification delay of carpal and metacarpal/phalanx bones.

Conclusion: Knowledge of the neuroimaging, skeletal and clinical spectrum of KBG syndrome will improve its detection rate and the prediction of its features, thus improving patient care.

16h30 - DEEP PHENOTYPING IN 7 NEW PATIENTS WITH MAP3K7 VARIANTS: FROM CARDIOSPONDYLOCARPOFACIAL TO FRONTOMETHAPYSEAL DYSPLASIA TYPE

Presenting author: Irene Valenzuela

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Introduction: *MAP3K7* heterozygous variants were recently reported to cause cardiospondylocarpofacial syndrome (CSCF) (OMIM 157800) and frontomethapyseal dysplasia type 2 (FMD2) (OMIM 617137). To date only 8 molecularly confirmed patients with CSCF and 20 with FMD2 have been reported. We compared and reviewed the clinical and







molecular findings in previously reported *MAP3K7* patient's cases with the present ones to better delineate the phenotype of CSCF. Our work expands the phenotypic and molecular spectrum of patients with *MAP3K7* variants.

Material and Methods: Here we report seven further patients from four unrelated families with heterozygous variants in *MAP3K7*. Four patients with clinical diagnosis of CSCF and three with FMD2. The molecular diagnosis in the probands of CSCF was uncovered by WES reanalysis and by first WES analysis in the FMD2 family. The four variants detected in the three families as responsible of the patient's phenotype are novel.

Results: Main clinical characteristics of our patients with CSCF include joint laxity (4/4), valvular dysplasia (3/4), skeletal findings (2/4), short stature (2/4) and hearing impairment (2/4). One patient presented in infancy with rectal prolapse and Diaphragmatic eventration findings not previously reported in CSCF patients. Dysmorphic features shared by the four patients are epicanthus, full cheeks and bulbous nasal tip in infancy. CSCF may overlap with the phenotypes of EDS and Noonan syndrome, suggesting that this finding may contribute to diagnosing CSCF. Main clinical characteristics of the three patients with FMD2, members of the same family, include prominent supraorbital ridges (3/3), small pointed chin (3/3), flexion contracture of elbows (3/3), interphalangeal joint contracture (3/3), aortic root dilation (1/3), keloid formation (1/3). The four missense variants detected are novel. The variants identified in CSCF patients are c.143G>A (p.Gly48Glu), c.146T>G;p.(Val49Gly), c.801G>T;p.(Trp267Cys) and c.548A>G; (p.Gln183Arg) the variant identified in the FMD2 family.

Conclusions: The inclusion of new patients with pathogenic variants in *MAP3K7* increases the knowledge of mutational spectrum and it's essential to delineate the phenotype of this allelic spectrum.

16h45 - CLINICAL EVOLUTION OF FOUR NEW PATIENTS WITH 3M SYNDROME

Presenting author: Anna Maria Cueto-González

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Background/Objectives: Pathogenic homozygous or compound heterozygous variants in the OBSL1, CUL7 and CCDC8 genes have been associated with 3M syndrome (Miller, McKusick and Malvaux) (ORPHA 2616; OMIM 273750, 612921 and 614205). Is characterized by severe growth retardation of prenatal onset and postnatal period and particular phenotypic and skeletal characteristics with normal intelligence, but hypogonadism may be present in some males. The phenotypes of the three genes overlap and a clear genotype-phenotype







correlation is not described, but the three share common characteristics that can help their suspected diagnosis

Material and methods: Here we report four patients (two females and two males) from four unrelated families with homozygous or compound heterozygous variants in OBSL1, CUL7 and CCDC8 genes. Three of them were born from consanguineous parents from Morocco (n=2) and Pakistan. The non-consanguineous was from Spain. All of them were diagnosed by whole-exome sequencing (WES) with clinical suspicion of this entity.

Results: WES identified homozygous variants in OBSL1 (n=1), CCDC8 (n=1) and CUL7 (n=1) were detected in the consanguineous families. The Spanish non-consanguineous family showed compound heterozygous variants in OBSL1.

All cases presented clinical manifestations during the prenatal period (in three cases with presented short long bones and in one with IURC). At birth, all patients presented head circumference (HC) within normal percentiles, but with length lower than -2.7 SD (being in one of the cases of -6'1SD). During growth the length has stagnated in all these patients, being between -3.81 and -8.86SD, but maintaining a relative macrocephaly (in most cases within normal parameters, between p43 and -2.62SD). Addionatlly, all patients presented triangular face, wide foreahead, anteverted nares, Joint hypermobility, short hands, prominent heels and short thorax. So far all have normal development and intelligence.

Two diagnosed during the first year of life and two at 6 and 10 years.

Conclusions: In addition to the importance of taking a good clinical history and physical examination at a given time, assessing the clinical course and growth from the neonatal period until we observe the patient can help guide the genetic diagnosis. Moreover, radiographic findings can also help in the differential diagnosis. This diagnosis is being useful for genetic counseling, as well as for possible treatments, given that insensitivity to growth hormone and/or IGF-I has been described.

17h00 - 3M SYNDROME IN TWO FETUSES: PRENATAL DESCRIPTION OF A RARE SKELETAL DYSPLASIA

Presenting author: Claire Beneteau

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3M syndrome is characterized by severe pre- and postnatal growth retardation, typical facial features, and normal intelligence. Homozygous or compound heterozygous pathogenic variants in either *CUL7*, *OBSL1*, or *CCDC8* have been identified. Most individuals are diagnosed postnatally and only few clinical data are available on fetal presentations.

We report antenatal and autopsy data of two unrelated fetuses with 3M syndrome and *CUL7* pathogenic variants. During pregnancy, nuchal translucency was increased to 3 cm for one fetus. At the 2nd and 3rd ultrasounds, both fetuses showed growth retardation (with normal head circumference or macrocephaly), thin and short bones without angulation or fracture, and craniofacial anomalies (prominent forehead, depressed nasal root, upturned nose, prominent philtrum, and protrusion of the ocular globes). At autopsy, bilateral ocular anomalies with corneal edema and congenital glaucoma were revealed in one of the fetus. Next-generation sequencing of 119 genes involved in congenital ophthalmologic abnormalities did not reveal any pathogenic variant. Does congenital glaucoma represent an expansion of the phenotypic spectrum of the 3M syndrome or is it an incidental association?

Next generation sequencing identified compound heterozygous pathogenic variants in *CUL7* with three novel pathogenic variants: two nonsense variants (NM_014780.4 : c.938G>A, p(Trp33*) ; c.1802C>G, p(Ser601*)) and one frameshift (c.79dup, p(Arg27Profs*7)).

We emphasize here that thin bones outside the context of fetal akinesia can guide the etiological diagnosis. 3M syndrome is a rare disease. In clinical practice, skeletal dysplasia is evoked by antenatal ultrasounds' features. Autopsy results sometimes allow the diagnosis but it remains difficult and is most often made by next generation sequencing. Given the genetic heterogeneity of skeletal dysplasias, we believe that exome sequencing and other high-throughput technologies will further improve the diagnosis of fetal skeletal dysplasias to refine genetic counseling and allow prenatal or preimplantation genetic diagnosis if desired.

Figure I. 2nd trimester profile and face ultrasound of fetuses 1 (A) and 2 (B) showing a prominent forehead, depressed nasal root, upturned nose, prominent philtrum, and protrusion of the ocular globes.

Figure 2. X rays and CT scans of fetuses 1 (A) and 2 (B). Short and thin bones are noted, with no curvature, fracture, or enlargement of the metaphyses. The iliopubic branches are present.

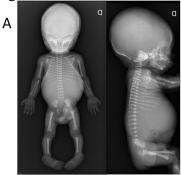




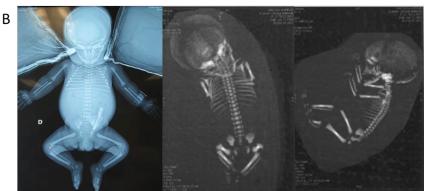




Figure II.







17h15 - TWO AFFECTED BROTHERS WITH TSUKAHARA SYNDROME PRESENT WITH A HOMOZYGOUS DELETION IN PUS7

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Tsukahara syndrome (MIM 603438) is a very rare disorder characterised by the association of bilateral radio-ulnar synostosis, microcephaly, short stature, scoliosis and mild to severe intellectual disability. Since the initial description by Tsukahara *et a.l* in 1995, less than 10 families have been reported. Autosomal recessive and X-linked dominant inheritance have been suspected while, so far, no known molecular etiology has been identified in this syndrome.

Intellectual developmental disorder with abnormal behavior, microcephaly and short stature (IDDABS) is an autosomal recessive disorder caused by homozygous loss of function variants in *PUS7* (MIM 616261). The gene encodes the RNA-independent pseudouridylate synthase 7, an enzyme implicated in post transcriptional modification of RNA and playing an important role in control of gene expression. To date, 8 unrelated consanguineous families have been described. All patients presented with short stature and poor weight, developmental delay, poor or absent speech, moderate to severe intellectual disability and progressive microcephaly. Additional features







consisted of behavioral abnormalities such as aggressivity, injurious behavior and short temper, with variable dysmorphic features including short and smooth philtrum, down slanting palpebral fissures and epicanthal folds, broad nasal root, full lips with everted lower lip and dental anomalies.

We describe a consanguinous family originating from Morocco in which two brothers are suspected of Tsukahara syndrome, a clinical diagnosis we made in 2007 based on typical phenotype associating microcephaly, severe intellectual disability and bilateral radio-ulnar synostosis. Whole exome sequencing was recently performed in both affected boys and their parents. CNV analysis of exome data suggested a deletion of the exon 15 (in a total of 16 exons) of *PUS7* in the affected patients. Using droplet digital PCR, we confirmed a homozygous deletion of exon 15 in *PUS7* in the boys, present in heterozygous state in their parents, in healthy sister and in healthy brother. This deletion has been previously reported in another Moroccan patient with IDDABS. However, radio-ulnar synostosis was not reported in this patient.

In conclusion, this is the first description of a molecular etiology found in two patients with clinical diagnosis of Tsukahara syndrome. We discuss the clinical features of this syndrome and compare it to IDDABS. Finally, we broaden the phenotype related to pathogenic variants in *PUS7*.

18h00 - SESSION 2: SKELETAL DYSPLASIA (Chair: Antonio Martinez-Monseny)

18h00 - A RARE LYSOSOMAL STORAGE DISEASE DUE TO NOVEL ARSK MUTATION IN TWO SIBLINGS

Presenting Author: Dilek Uludağ Alkaya

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Introduction: Mucopolysaccharidoses (MPS) are a group of diseases characterized by disruption of glycosaminoglycan (GAG) degradation due to mutations in genes encoding lysosomal enzymes. The phenotype may differ according to the organ involvement (skeletal, brain, liver, spleen, cardiac valves, eye) where accumulation occurs. A new type of MPS associated with deficiency of arylsulfatase K (ARSK) enzyme which was first reported in 2013 as a new lysosomal sulfatase, exhibiting glucuronate-2-sulfatase activity as needed for the degradation of heparan sulfate (HS), chondroitin sulfate (CS) and dermatan sulfate (DS). There are only 4 cases reported from Austria in 2021. Herein, we present two siblings with skeletal features and waddling gait; and were diagnosed with MPS type X.

Clinical Features: The older sibling (case 1), born in May 2003, was referred to us when she was 11 years and 9 months old, with two years of waddling gait and right hip pain. She was







the first child born of consanguineous marriage. Her brother (case 2), was born in June 2007, admitted to our clinic at the age of 9 years. He had a complaint of limitation in the knee joint and had a history of 3 mild trauma-related fractures. Both of their birth weight, height and head circumference were within normal limits. Neuromotor developments were in accordance with their age. Height of case 1 was 144 cm (-1,13 SDS) and 150 cm (-2,23 SDS) at initial and last examination (age of 19) respectively. Her sitting height / height ratio was 0.46. She described pain with flexion and abduction in her right hip, and she could not sit cross-legged. Swan neck deformity was noted in the 3rd, 4th and 5th fingers of the right hand. Other system examinations were normal. Case 2's height was 132 cm (-0,1 SDS) and 162 cm at initial and last (age of 15) examination, respectively. The patients' serum calcium, phosphorus, alkaline phosphatase, vitamin D and parathormone values were within normal limits. In radiographs of case 1; 4th metacarpal was short. Platyspondyly and double contour sign were detected in the vertebrae. The right femoral head was small, and the neck was short. Vertical striping in the distal metaphysis of the femur was noticed. Anterior beaking and epiphysis irregularity of the vertebrae, and vertical striping in the distal metaphysis of the femur were observed in the case 2's radiographs. Blood enzyme levels for lysosomal storage diseases and GAG levels checked in blood and urine were normal in both siblings. After MATN3 and COL9A1 gene analyzes were detected normal, WES analysis was performed to case 1, a homozygous c.427G>T mutation was found in exon 4 of ARSK. Case 2 was also homozygous and both parents were heterozygous for the same mutation. The mutation was found to be pathogenic in databases.

Discussion: The absence of coarse face and deformity of metacarpals, which are well-known physical examination findings for MPS in our patients, made us think of different diseases in the differential diagnosis in the first place.

Conclusion: Mucopolysaccharidoses type 10 due to ARSK mutation is an extremely rare entity, and it should be considered in patients whose coarse facial appearance is not very prominent and whose clinic cannot be fully established with known MPS types.



18h15 - VAN MALDERGEM SYNDROME TYPE 2: AN EXTREMELY RARE SYNDROMIC DISORDER WITH INTELLECTUAL DISABILTY AND SKELETAL PHENOTYPES

Presenting Author: Ceren Ayça Yıldız

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Introduction: Van Maldergem syndrome (VMS) is an autosomal recessive disorder characterized by distinct facial features (hypertelorism, telecanthus, ptosis, maxillary hypoplasia, oligodontia, microtia), hearing loss, hand anomalies, and intellectual disability. Biallelic variants in genes *DCHS1* and *FAT4* cause VMS type 1 and VMS type 2, respectively. Herein, we report a Turkish patient with a novel *FAT4* variant.

Patient: The patient was referred to our department due to dysmorphic face and developmental delay at the age of 5 months. She was the first child of the first cousin's parents. Family history was unremarkable. Polyhydramnios was detected in the pregnancy. She was born at term with a birth weight of 2000 gr. In the initial physical examination, her weight, length and head circumference were 4 kg (-4.4 SD), 57cm (-3.13SD), and 37 cm (-4.03 SD), respectively. She had large anterior fontanelle, microtia, proptotic eyes, epicanthus, telecanthus, depressed nasal bridge, low set-posteriorly rotated ears, short philtrum, hypertrophic gingiva, and camptodactyly. Neuromotor milestones were delayed. She achieved head control at 4 months, sitting without support at 2 years, and walking at 3 years of age. She had her first words at 3 years of age. The eruption of permanent teeth was delayed. Severe mixed hearing loss was detected at 3.5 years, and she started using hearing aid. Eye examination revealed vascular tortuosity. Mitral valve prolapsus detected on echocardiography. She had an afebrile convulsion at 15 years of age.

Electroencephalography and cranial magnetic resonance imaging were normal. She also had lower extremity edema at 15 years of age and serum albumin, fecal alpha 1 antitrypsin, and urine analysis were found normal. Radiographs revealed wormian bones, opened coronal and lambdoid sutures, thickened skull base, and wide 2-3 metacarpals at 15 years of age. At the last examination at 17 years of age, her weight, length, and head circumference were 46.2kg (-1,9SD), 152cm (-1,8SD), 51cm (-1,5SD), respectively. In molecular studies, chromosome and microarray analyses were normal. Whole exome sequencing was performed and a novel homozygous variant (NM_001291285: c.9670G>A) was identified in the *FAT4* gene.

Conclusion: VMS is a clinically recognizable syndrome due distinct facial features. To date, thirteen VMS type 2 patients have been reported. Our report expands the phenotypic spectrum of the syndrome.

18h30 - LESSER KNOWN EFFECTS: A CASE OF OSTEOCHONDRODYSPLASIA FOLLOWING HAEMATOPOIETIC STEM CELL TRANSPLANTATION

Presenting author: Sally-Ann Lynch

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There is an emerging body of evidence showing that young patients, post haematopoietic stem cell transplantation (HSCT), can develop skeletal changes that mimic an osteochondrodysplasia process¹. The key discriminator is that these children have had otherwise normal growth and skeletal development before the therapeutic intervention (HSCT), typically for a haematological malignancy.

Skeletal dysplasias are a heterogeneous group of disorders that will generally result in one or more of short stature, abnormal skeletal proportions and specific features on radiographic imaging. They are typically genetic and Mendelian in origin but a smaller number may be non-genetic in origin².

Herein we present that case of a boy who underwent HSCT for haemophagocytic Lymphohistiocytosis (HLH) aged 2 years. He had a stormy clinical course with and acquired brain injury that is thought to be related to the treatment which has resulted in cognitive impairment and epilepsy. Following Intervention with HSCT this boy's growth has severely decelerated (stature less than 1st centile matched for age) and he has developed a spondyloepiphyseal dysplasia.

Clinical examination shows relative lengthening of arms compared to his overall height. There is a pectus excavatum. There is appreciable truncal and limb hypotonia. There is mild joint laxity. There is bilateral genu valgum, worse on the left side.

All genetic investigations to date including an ArrayCGH and Trio Whole Exome Sequence have been non-diagnostic and there is no relevant family history; he is from a non-consanguineous white Irish background.

Following discussion of his case with the authors who originally reported this association, it was felt that this boy's phenotype and clinical history is consistent with a non-genetic origin to his osteochondrodysplasia, and that in light of his history, HSCT is the key aetiological factor responsible.



References :1) Botto et al. 2020 DOI: 10.1002/ajmg.a.62021, 2)Mortier et al. 2019 DOI: 10.1002/ajmg.a.61366

Bilateral acetabular dysplasia is noted. Epiphyseal changes are present in the proximal and distal femora, consistent with the underlying diagnosis of spondyloepiphyseal dysplasia. There is bilateral genu valgum. Reduced vertebral body height is also noted in the partially imaged lumbar spine. All images displayed with patient's consent and approval.





18h42 - NOVEL VARIANT IN SOX9 ASSOCIATED TO MILD CAMPOMELIC DYSPLASIA PHENOTYPE

Presenting author: Purificación MARÍN REINA

Authors: Marin-Reina P¹, Perez-Aytes A¹, Zuñiga Cabrera A², Novella Maestre E², Guasp Vizcaino M³, Salom Taverner M⁴

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XXX is a 4-year-old female from a non-consanguineous, spanish couple. Mother 32 year old; father 35 year old. A healthy brother 14 years old. Uneventful pregnancy. Delivery at 40 weeks gestation. Birth weight: 3.150 gm. Apgar 6/8. Due to the continued need for ventilatory support, as she was 4 months old, tracheostomy was performed. At birth, no dysmorphic features are reported and no bone abnormalities were seen on radiographs.

Physical examination at 11 months of age: Weight: 7.160 gm (p6) Height: 67,5 cm (p2) OFC: 49,5 cm (3,74SD). Frontal bossing, flat nasal bridge with anteverted nares, downslanting palpebral fissures, retrognathia, pectus carinatum, thoracic spinal kyphosis, mild hypotonia.

- Brain echography: Normal
- Cardiac echography: Ventricular septal defect
- Fibrobronchoscopy: Tracheal collapse
- Genomic Microarray: Normal female study (No pathogenic CNVs)
- X-ray: Sella turcica anteroposteriorly elongated, thoracic kyphosis, rest of the skeleton without abnormalities.

Due to short stature with spinal kyphosis, disproportionate OFC and laryngomalacia, a skeletal dysplasia was suspected. A molecular genetic study with a skeletal dysplasia panel was performed. Heterozygous variant c.313 G>T (p.Val105Phe) in SOX9 gene, associated to Campomelic dysplasia, was found. This is a novel variant not described in genetic databases, but in siliko analysis by informatic predictors permits to classify as probably pathogenic. Study in both parents was negative, and was assumed the variant appeared as the novo event in the patient.

In the follow-up, respiratory distress was improving and tracheotomy could be removed at age 2 year. The baby is now 4 year old, she assists ordinary school, need glasses because myopia and astigmatism, and has normal motor and cognitive skills for her age, assisting to normal school with children of her age. The placement of a thoracic splint for the kyphosis is planned.

Comment: Campomelic dysplasia (Orpha:140; MIM:114290) is a well known skeletal dysplasia being the more typical features: short stature with large head, short bowed limbs with presence of pretibial dimples (lower limbs are usually more affected), midface hypoplasia, respiratory distress, laryngomalacia, club feet, and sex reversal in 46, XY patients. In X-ray typical features are bowed femora and tibiae, dislocated hip, hypoplastic







scapulae, cervical spine anomalies, eleven pair of ribs, narrow and vertically oriented iliac wings, hypoplastic vertebral thoracic pedicles.

Our patient has short stature with large head, respiratory distress with laryngomalacia, and thoracic spine deformities, but lack many other typical findings of Campomelic dysplasia. Lack of typical bowed limbs is described as Acampomelic campomelic dysplasia (ACD). Seems that ACD is more frequently associated to patients with missense mutations or chromosomal rearrangements or deletions upstream SOX9. Our patient could be a case of ACD, but the lack of many other typical features make questionable the diagnosis.

DAY 2 – THURSDAY 14th OF SEPTEMBER

09h00 – SESSION 3: NEW SYNDROMES (Chair: Hilde Peeters)

09h00 - DIFFERENTIAL ALTERNATIVE SPLICING ANALYSIS TO LINK VARIATION IN ZRSR2 TO A NOVEL SYNDROME WITH ORAL, DIGITAL AND BRAIN ANOMALIES

Presenting author: Laurens Hannes

<u>Laurens Hannes</u>^{1, 2}, Marta Atzori¹, Elise Pelgrims¹, Ann Swillen^{1,2}, Alejandro Sifrim¹, Catia Attanasio¹, Jeroen Breckpot^{1, 2}

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ZRSR2, located on Xp22.2, is part of the minor spliceosome complex which recognises U12-type introns representing 0.35% of human introns. Minor spliceosome defects have been associated with developmental disorders. Somatic mutations in ZRSR2 are found in myelodysplastic syndromes, germline variation in ZRSR2 has not been implicated in impaired human development yet.

We describe a 24-months-old boy presenting upper limb bilateral postaxial polydactyly, doubled first ray of the feet, a tongue nodule, seizures, pituitary abnormalities and polymicrogyria. A maternal uncle died neonatally with holoprosencephaly, polydactyly and ambiguous genitalia. A son of a maternal aunt of the mother died prenatally with brain and limbs anomalies. Unfortunately DNA of these male relatives was not preserved. Whole exome sequencing and segregation analysis of 6 informative males was performed, followed







by whole transcriptome RNA-SEQ on fibroblasts from the extra digit and tongue nodule, and on EBV cell lines of the index and mother.

WES showed a maternally inherited frameshift c.1207_1208delAG (p.Arg403Glyfs*24) in the last exon of ZRSR2, compatible with X-linked recessive inheritance. This variant is absent in reference databases, but has been described as a variant of unknown significance in a family with 5 male foetuses with holoprosencephaly. Whole transcriptome differential expression and alternative splicing analysis of minor spliceosome gene targets showed a similar effect on U12-dependant splicing as seen in somatic ZRSR2 mutations in myelodysplastic syndrome.

Genetic and functional data associate this ZRSR2 variant to a novel syndrome with variable expression of oral, digital and brain (holoprosencephaly) anomalies.

09H15 - HETEROZYGOUS PATHOGENIC VARIANTS INVOLVING *CBFB* CAUSE A NEW SKELETAL DISORDER RESEMBLING CLEIDOCRANIAL DYSPLASIA

Presenting author: Tessi Beyltjens

Tessi BEYLTJENS 1 , Eveline BOUDIN 1 , Nicole REVENÇU 3 , Nele BOECKX 1 , Miriam BERTRAND 4 , Tobias HAACK 4 , Axel WEBER 5 , Eleni BILIOURI 5 , Mateja VINKŠEL 6 , Anja ZAGOŽEN 6 , Borut PETERLIN 6 , Shashidhar PAI 7 , Aida TELEGRAFI 8 , Lindsay B. HENDERSON 8 , Courtney ELLS 9 , Lesley TURNER 9,10 , Wim WUYTS 1 , Wim VAN HUL 1 , Gretl HENDRICKX 1,2 *, Geert MORTIER 1,2,11 *

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Background: Cleidocranial dysplasia (CCD) is a rare skeletal dysplasia with significant clinical variability. CCD patients typically present with delayed closure of fontanels and cranial sutures, dental anomalies, clavicular hypoplasia or aplasia and short stature. RUNX2 is currently the only known disease-causing gene for CCD, but several studies have suggested locus heterogeneity.







Methods: The cohort consists of eight subjects from five unrelated families partially identified through GeneMatcher. Exome or genome sequencing was applied and in one subject the effect of the variant was investigated at RNA level.

Results: In each subject a heterozygous pathogenic variant in CBFB was detected, whereas no genomic alteration involving RUNX2 was found. Three CBFB variants (one splice site alteration, one nonsense variant, one 2bp duplication) were shown to result in a premature stop codon. The precise effect of the two other variants, one intragenic deletion and one splice site variant, could not be determined but most likely result in either a shortened or absent protein. Affected individuals showed similarities with RUNX2-related CCD, including dental and clavicular abnormalities. Normal stature and neurocognitive problems were however distinguishing features. CBFB codes for the core-binding factor β subunit (CBFβ) which can interact with all RUNX proteins (RUNX1; RUNX2; RUNX3) to form heterodimeric transcription factors. This may explain the phenotypic differences between CBFB related CCD and RUNX2-related CCD.

Conclusion: We confirm the previously suggested locus heterogeneity for CCD by identifying five novel pathogenic variants in CBFB in a cohort of eight individuals with clinical and radiographic features reminiscent of CCD.

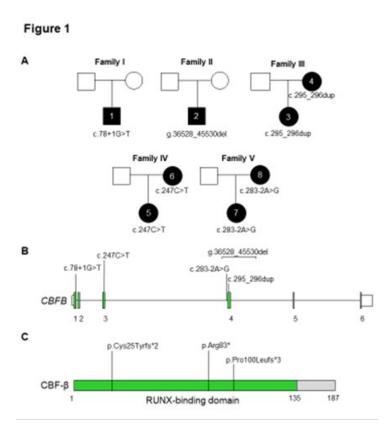
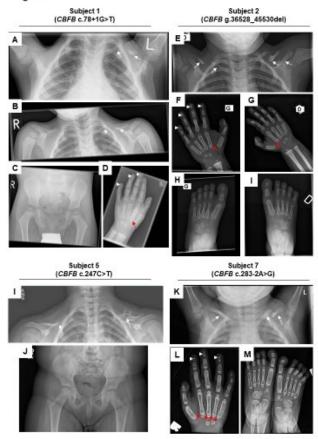








Figure 2



09h30 - SEMA6B VARIANTS CAUSE INTELLECTUAL DISABILITY AND ALTER DENDRITIC SPINE DENSITY AND AXON GUIDANCE

Presenting author: Annick Toutain

Amélie Cordovado¹, Martina Schaettin², Médéric Jeanne¹³, Veranika Panasenkava¹, Anne-Sophie Denommé-Pichon⁴,⁵, Boris Keren⁶, Cyril Mignot⁶, Martine Doco-Fenzyժ, Lance Rodan³,⁶, Keri Ramsey¹⁰, Vinodh Narayanan¹⁰, Julie R. Jones¹¹, Eloise J. Prijoles¹², Wendy G. Mitchell¹³, Jillian R. Ozmore¹⁴, Kali Juliette¹⁵, Erin Torti¹⁶, Elizabeth A. Normand¹⁶, Leslie Granger¹ժ, Andrea K. Petersen¹ժ, Margaret G. Au¹³, Juliann P. Matheny¹³, Chanika Phornphutkul¹⁶, Mary-Kathryn Chambers²⁰, Joaquín-Alejandro Fernández-Ramos²¹, Eduardo López-Laso²¹, Michael C. Kruer²²,²³, Somayeh Bakhtiari²²,³³, Marcella Zollino²⁴,²⁵, Manuela Morleo²⁶,²ð, Giuseppe Marangi²⁴,²⁵, Davide Mei²³, Tiziana Pisano²³, Renzo Guerrini²³, Raymond J. Louie¹¹, Anna Childers¹¹, David B. Everman¹¹, Betrand Isidor²⁶, Séverine Audebert-Bellanger³⁰, Sylvie Odent³¹, Dominique Bonneau³², Brigitte Gilbert-Dussardier³³, Richard. Redon³⁴, Stéphane Bézieau³⁴,³⁵, Frédéric Laumonnier¹, Esther T. Stoeckli², Marie-Laure Vuillaume¹,³, Annick Toutain¹,³

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In this study, we collected 14 SEMA6B heterozygous variants in 16 unrelated patients referred for intellectual disability to different centres. Whereas until now SEMA6B variants have mainly been reported in patients with progressive myoclonic epilepsy, our study indicates that the clinical spectrum is wider, and also includes non-syndromic intellectual disability without epilepsy or myoclonus.

To assess the pathogenicity of these variants, we performed in vitro functional studies. Overexpression of some mutated forms of Sema6b in HEK293T cells and in primary neuronal cultures showed a subcellular mislocalisation of SEMA6B protein and a reduced spine density due to loss of mature spines in neuronal cultures. shRNAs targeting Sema6b in neuronal cultures showed that Sema6b knock-down also impairs spine density and spine maturation.

In addition, we conducted in vivo rescue experiments in chicken embryos with the selected mutated forms of Sema6b expressed in commissural neurons after knock-down of endogenous *SEMA6B*. We observed that expression of these variants in commissural neurons fails to rescue the normal axon pathway.

In conclusion, identification of *SEMA6B* variants in patients presenting with an overlapping phenotype with intellectual disability, and functional studies highlight the important role of SEMA6B in neuronal development, notably in spine formation and maturation, and in axon guidance. This study adds *SEMA6B* to the list of intellectual disability-related genes.

09h45 - HETEROZYGOUS VARIANTS IN CTR9, WHICH ENCODES A MAJOR COMPONENT OF THE PAF1 COMPLEX, ARE ASSOCIATED WITH A NEURODEVELOPMENTAL DISORDER

Presenting author: Marije Meuwissen

Marije Meuwissen^{1,*}, Aline Verstraeten^{1,*}, Emmanuelle Ranza^{2,*}, Justyna Iwaszkiewicz³, Maaike Bastiaansen¹, Ligia Mateiu¹, Merlijn Nemegeer¹, Josephina A.N. Meester¹, Alexandra Afenjar⁴, Michelle Amaral⁵, Diana Ballhausen⁶, Sarah Barnett⁷, Magalie Barth⁸, Bob Asselbergh^{9,10}, Katrien Spaas^{9,10}, Bavo Heeman^{11,10}, Jennifer Bassetti¹², Patrick Blackburn¹³, Marie Schaer¹⁴, Xavier Blanc², Vincent Zoete^{3,15}, Kari Casas¹⁶, Thomas Courtin¹⁷, Diane Doummar¹⁸, Frédéric Guerry², Boris Keren¹⁷, John Pappas¹⁹, Rachel Rabin¹⁹, Amber Begtrup²⁰, Marwan Shinawi²¹, Anneke T. Vulto-van Silfhout²², Tjitske Kleefstra²², Matias Wagner^{23,24}, Alban Ziegler⁸, Elise Schaefer²⁵, Benedicte Gerard²⁶, Charlotte I. De Bie²⁷, Sjoerd J.B. Holwerda²⁷, Mary Alice Abbot²⁸, Stylianos E. Antonarakis², Bart Loeys^{1,22}

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PURPOSE: CTR9 is a subunit of the PAF1 complex (PAF1C), that plays a crucial role in transcription regulation by binding of CTR9 to RNA polymerase II. It is involved in transcription-coupled histone modification by promoting H3K4 and H3K36 methylation. We describe the clinical and molecular studies in 13 probands harboring likely pathogenic *CTR9* missense variants collected through GeneMatcher.

METHODS: Whole exome sequencing was performed in all individuals. CTR9 variants were assessed by three-dimensional modelling of the activated human transcription complex Pol II-DSIF-PAF-SPT6 and the PAF1/CTR9 complex. H3K4/H3K36 methylation analysis, mitophagy assessment based on tetramethylrhodamine ethyl ester perchlorate immunofluorescence and RNA-sequencing in skin fibroblasts from 4 patients was performed.

RESULTS: Common clinical findings were variable degrees of intellectual disability, ranging from mild to severe, hypotonia, speech delay, coordination difficulties, tremor and joint hyperlaxity. Behavioral abnormalities including autism spectrum disorder, aggression and ADHD and psychiatric disorders with psychotic episodes and mood disorders were reported in a subset of cases. Brain MRI, performed in 6 cases, showed a-specific abnormalities in 2, comprising delayed myelination, short/ thin corpus callosum and ventricular dilatation. Variable non-specific, subtle dysmorphic features were noted, recurrent features include hypertelorism, micro/retrognathia and a broad, flat nasal bridge. Other findings included cardiac abnormalities, including infantile thoracic aortic aneurysm, ventricular septal defect, mild pulmonary valve stenosis and supravalvular aortic stenosis, and failure to thrive/feeding problems.

For eleven *CTR9* variants, *de novo* occurence was demonstrated. Three-dimensional modelling predicted a likely disruptive effect of the variants on local CTR9 structure and







protein interaction. Additional studies in fibroblasts did not unveil the downstream functional consequences of the identified variants.

CONCLUSION: We describe a neurodevelopmental disorder caused by (mainly) *de novo* variants in *CTR9*, likely affecting PAF1C function.

10h00 - ESTABLISHING *DE NOVO* MISSENSE VARIANTS IN *NSF* AS A CAUSE FOR INFANTILE EPILEPTIC ENCEPHALOPATHY WITH BURST-SUPPRESSION PATTERN

Presenting author: Sarah Schuhmann

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Intracellular vesicle transport and membrane fusion are essential for several biological processes including the secretion of hormones and neurotransmitters. Deregulation of these pathways was implicated in neurological diseases and epileptic encephalopathies. The ATPase N-ethylmaleimide-sensitive factor (NSF) plays an important role in membrane trafficking. Upon interaction with its receptors and calcium, NSF regulates the fusion of vesicles with target membranes in all eukaryotic cells. A *Drosophila* model carrying a missense mutation in the homolog of *NSF*, *comatose* (*comt*), developed temperature-dependent electrical bursts in flight muscles which resemble human febrile seizures. Downregulation of NSF in neuronal cell lines induced enhancement of neurite outgrowth, a structural change similar to that following epilepsy. These results provided the first evidence that variants in *NSF* could be related to the development of epilepsy.

Recently, two unrelated Japanese individuals harbouring *de novo* heterozygous missense variants in *NSF* were reported for the first time. Both of them presented with infantile epileptic encephalopathy characterized by a burst suppression pattern in the electroencephalogram (EEG). The individuals further showed frequent vomiting in the neonatal period and profound intellectual disability. One of them died in infancy of respiratory failure. The *NSF*-associated epileptic encephalopathy was listed in OMIM as developmental and epileptic encephalopathy 96. Functional studies in *Drosophila* indicated a dominant-negative effect of the identified *NSF* variants.

Here we describe the third patient, a 5-month-old female individual from healthy non-consanguineous parents presenting with severe infantile epileptic encephalopathy. After birth, she showed failure to thrive requiring gastric tube and developed recurrent vomiting. Lethargy and muscular hypotonia were also reported. At the age of 10 days the first seizures were observed, at the age of 3 months she had up to 100 seizures per day and EEG showed a burst-suppression pattern which later evolved to hypsarrythmia. Social development and







motor milestones were significantly delayed. Diagnostic trio exome sequencing revealed no disease causing variants. In a research setting we identified a *de novo* heterozygous missense variant c.695G>A, p.(Arg232Gln) in *NSF*, neither previously described in affected individuals nor listed in genetic databases. Similar to the previously described pathogenic changes, the identified missense variant was located in the AAA domain (D1) of the NSF protein.

Describing the third reported case worldwide with a *de novo* pathogenic variant in *NSF*, we establish *NSF* as an infantile epileptic encephalopathy gene. We also highlight the burst-suppression pattern in EEG during the neonatal period as main feature of NSF-associated epileptic encephalopathy.

10h15 - RUBINSTEIN-TAYBI SYNDROME: A MODEL OF EPIGENETIC DISORDER

Presenting author: Julien Van Gils

<u>Julien Van Gils</u>¹, Sadegheh Haghshenas^{2,3}, Frederique Magdinier⁴, Patricia Fergelot¹, Bekim Sadikovic^{2,3} and Didier Lacombe¹

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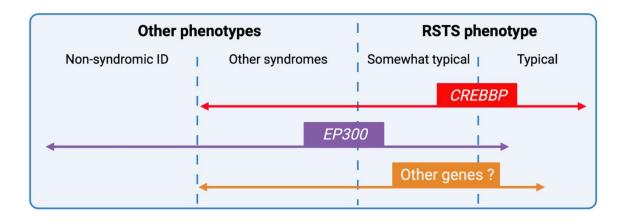
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The Rubinstein-Taybi syndrome (RSTS) is a rare congenital developmental disorder characterized by a typical facial dysmorphism, distal limb abnormalities, intellectual disability, and many additional phenotypical features. It occurs at between 1/100,000 and 1/125,000 births. Two genes are currently known to cause RSTS, CREBBP and EP300, mutated in around 55% and 8% of clinically diagnosed cases, respectively. To date, 500 pathogenic variants have been reported for the CREBBP gene and 118 for EP300. These two genes encode paralogs acting as lysine acetyltransferase involved in transcriptional regulation and chromatin remodeling with a key role in neuronal plasticity and cognition. Because of the clinical heterogeneity of this syndrome ranging from the typical clinical diagnosis to features overlapping with other Mendelian disorders of the epigenetic machinery, phenotype/genotype correlations remain difficult to establish. In this context, the definition of a specific DNA methylation episignature and more specifically, our study of acetylation and transcriptomic profiles on the iPSC-derived-neurons model will allow the deciphering of the patho-physiological process underlying this disease and improve the diagnostic efficiency but also open novel therapeutic perspectives. These data highlight the epigenetic regulation of RSTS as a model of chromatinopathy.









11h00 - SESSION 4: MORPHOMETRICS & MOLECULAR GENETICS (Chair: Pablo Lapunzina)

11h00 – INVITED TALK: HILDE PEETERS, 3D FACIAL MORPHOMETRICS FOR DYSMORPHOLOGISTS

11h45 - OBJECTIVE STUDY OF FACIAL DYSMORPHISM USING SPATIALLY DENSE 3D FACIAL PHENOTYPING

Presenting author: Michiel Vanneste

Michiel VANNESTE^{1,2}, Harold MATTHEWS^{1,2,3}, Peter CLAES^{1,2,3,4}, Hilde PEETERS¹.

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Background: A comprehensive assessment of the facial phenotype is essential in dysmorphology. Recognizing a typical facial gestalt facilitates clinical and molecular diagnosis and accurate facial phenotyping is a cornerstone of syndrome nosology and the study of genotype-phenotype correlations. However, the objective analysis of the facial phenotype remains underdeveloped. Three-dimensional (3D) photographs allow for an easy capture of facial morphology and subsequent analysis. In this work we describe recent advances in the







analysis of 3D facial photographs for the objective assessment of the facial phenotype and illustrate different applications in the study of facial dysmorphism.

Methods and results: In 2019 our lab released the Meshmonk toolbox for non-rigid facial registration¹. This allows a 3D image to be measured at a standardized set of densely sampled points, allowing 3D facial images to be compared and combined meaningfully. In 2021 we derived the first '3D facial growth curves' combining data from a large database of individuals of European descent into the first openly available normative reference models for 3D facial shape². These allow the assessment of an individual face relative to an age and sex appropriate normative reference and generate their 'facial signature', an objective description of facial dysmorphism. These can then be employed in group level analyses to describe the typical facial signature of a syndrome and study the phenotypic relationships among syndromes.

We explored these advancements by performing individual and group-level phenotypic analysis on a sample of 3D photographs of individuals with diverse dysmorphic disorders. Individual facial signatures highlighted known syndromic facial traits and we objectively assessed within- and between group directional variation and variation in phenotypic severity.

Conclusion: We presented recent advances in 3D facial phenotyping for the objective assessment of facial dysmorphism and show their application in the study of facial dysmorphism for clinical and research purposes.

References

- 1. White, J. D. et al. Sci. Rep. 9, (2019).
- 2. Matthews, H. S. et al. Sci. Rep. 11, 12175 (2021).

12h00 - GESTALTMATCHER RESEARCH PLATFORM FACILITATES THE NOVEL GENE-PHENOTYPE EXPLORATION

Presenting author: Jing-Mei Li

<u>Jing-Mei Ll¹</u>, Luisa AVERDUNK², Cristopher MAK³, Hellen LESMANN¹, Tori Jean PANTEL¹, Tom KAMPHANS⁴, Wolfgang MEISWINKEL⁴, Peter KRAWITZ¹, Tzung-Chien HSIEH¹

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Introduction: The next-generation phenotyping (NGP) approaches for syndromology, such as GestaltMatcher [1], have learned facial representations of multiple disorders by training on thousands of patient photos. GestaltMatcher can predict the disorder and quantify the similarity between patients, enabling novel gene-phenotype exploration. To improve the usability, we proposed the GestaltMatcher research platform to provide a user-friendly interface to upload patients, select patients from existing publications, and conduct gene-







phenotype association experiments. We further showed how to utilize GestaltMatcher for the lumping and splitting analysis.

Methods: We built a research platform in GestaltMatcher Database (GMDB). GMDB currently contains 5510 patients with 573 different disorders from 1481 publications. Users can analyze their patients and include the patients from publications in GMDB in their experiments. The research platform supports the GestaltMatcher approach to calculate the similarities among the selected cohort, generating the matrix of pairwise distances and the figure of t-SNE for the two-dimensional visualization. We selected two cohorts as examples: Cohort-1 consists of five patients with disease-causing mutations in *Gene-X*, and Cohort-2 contains 33 patients with the disease-causing mutations in *Gene-Y*.

Results: We first showed the lumping analysis by Cohort-1. With the matrix of pairwise distances and the figure of t-SNE, we proved that the facial phenotype of the five patients in Cohort-1 is similar to Rothmund-Thomson syndrome (OMIM:268400). The result further suggests that the phenotype caused by *Gene-X* can be merged into the phenotypic series of Rothmund-Thomson syndrome. Moreover, we performed the splitting analysis for Cohort-2. We validated that the facial phenotype of the ten patients with the mutations in the first exon of *Gene-Y* is different from the other 23 patients with the mutations in the second exon of *Gene-Y*. The patients in the first exon and the patients in the second exon formed two clear clusters. We concluded that the second exon of *Gene-Y* can cause a novel phenotype that has not been linked to *Gene-Y* yet.

Conclusion: GestaltMatcher research platform provides users with a user-friendly interface to explore the novel gene-phenotype association and facilitate the lumping and splitting analysis.

References: Hsieh, T.-C. et al. GestaltMatcher facilitates rare disease matching using facial phenotype descriptors. Nat. Genet. (2022)

12h15 - DEEPPRIVACY: A DEEP LEARNING FRAMEWORK FOR SYNTHESIZING DYSMORPHIC PORTRAITS TO PROTECT PATIENT PRIVACY

Presenting author: Tzung-Chien HSIEH

<u>Tzung-Chien HSIEH</u>¹, Alexander HUSTINX¹, Behnam JAVANMARDI¹, Jing-Mei LI¹, Hellen LESMANN¹, Tori Jean PANTEL¹, Silvan MERTES², Fabio HELLMANN², Elisabeth ANDRÉ², Shahida MOOSA³, Peter KRAWITZ¹

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Introduction: The high performance of next-generation phenotyping approaches depends on the size and diversity of the training dataset. Because collecting such a high-quality image dataset is challenging, the possibility of sharing data among different sites becomes crucial. However, since individuals are re-identifiable by their faces, it increases the difficulty in data sharing. The lack of sharable medical image datasets has become a massive limitation in pushing this research field forward. Therefore, we proposed DeepPrivacy to synthesize the faces with rare disorders to overcome the barrier to medical image sharing.

Methods: We compiled a dataset consisting of 6,584 frontal images with 204 different disorders from GestaltMatcher Database. This dataset is named as "real dataset." We trained the generative adversarial networks on the real dataset to learn facial dysmorphism and synthesized "synthetic dataset" of 6,584 faces with 204 rare disorders. We then trained the deep convolutional neural networks on the real and synthetic datasets separately to classify 204 disorders and benchmarked these two models on 615 test images.

Results: We first showed that the model trained on synthetic images achieved comparable performance as that trained on the real images. The dysmorphologists further confirmed that the key dysmorphic features were preserved in the synthetic images. Moreover, face verification proved that the synthetic images cannot re-identify the real patients. Lastly, we demonstrated how to synthesize a dysmorphic face from a healthy person (Figure 1). With this transform, clinicians can learn how the facial dysmorphic features change the healthy face.

Conclusion: We proved that synthetic facial images could be shared without privacy concerns. Moreover, facial portraits are still the best teaching material for clinicians in medical genetics. Therefore, beyond the deep learning purpose, it is also of interest to educate the next generation of physicians.

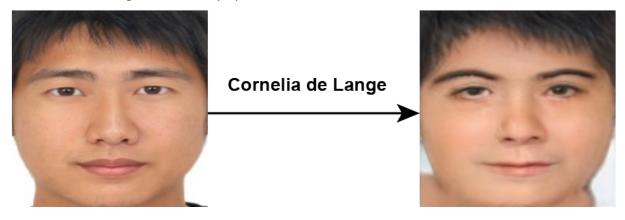


Figure 1: synthesize a face of Cornelia de Lange Syndrome from a healthy person.





12h30 – THREE PATIENTS WITH HYPERTRICHOSIS AND GINGIVAL HYPERPLASIA; ONE UNSOLVED

Presenting author: Pablo Lapunzina

Jair Tenorio-Castaño, Alejandro Parra, Natalia Gallego, Sergio Ramos, Alberto Ahijado, Elena Vallespín, Sixto García-Miñaur, María Palomares, Víctor Martínez-Glez, Julián Nevado, Fernando Santos, Marta Feito, Raúl de Lucas, Pablo Lapunzina.

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We report 3 patients with the clinical findings of generalized congenital hypertrichosis with gingival hyperplasia (MIM# 135400). Two boys and a girl are presented. One male patient is from Morocco and has a microdeletion of the 17q24.2-q24.3 region (samples of the parents unavailable). The second patient is a Spanish girl with a de novo microduplication of the 17q24.2-q24.3 band. The third patient is from Mexico and presents no molecular defect after an exhaustive work-up including karyotype, SNParray and array-CGH and WGS. We reinforce the clinical and facial findings of these patients, irrespective of their ethnic background; mainly the broad nose and the characteristic midfacial features. One patient remains without molecular confirmation opening the possibility of unreported additional mechanisms such as TADs or complex genomic rearrangements.

12h45 - DESCRIPTION OF TWO NEW CASES OF *AQP1* RELD PULMONARY ARTERIAL HYPERTENSION AND REVIEW OF THE LITERATURE

Presenting author: Natalia Gallego-Zazo

<u>Natalia Gallego-Zazo^{1,2,3}</u>, Alejandro Cruz-Utrilla^{4,5}, María Jesús del Cerro⁶, Nuria Ochoa Parra^{4,5}, Julián Nevado^{1,2,3}, Pedro Arias^{1,2,3}, Pablo Lapunzina^{1,2,3}, Pilar Escribano-Subias^{4,5,7} and Jair Tenorio-Castaño^{1,2,3}*

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Pulmonary arterial hypertension (PAH) is a severe clinical condition characterized by an increase in mean pulmonary artery pressure, which leads to a right ventricular hypertrophy and potentially heart failure and death. In the last several years, many genes have been associated with PAH, especially in idiopathic and heritable forms but also in associated forms.







Here we described the identification of two unrelated families in which *AQP1* variant was found from a cohort of 300 patients. The variants were identified by whole exome sequencing (WES). In the first family, the variant was detected in three affected members from a hereditary PAH, and in the second family the proband has PAH associated with scleroderma.

In addition, we have reviewed all cases published in the literature so far of patients with PAH and *AQP1* variants. Functional studies have led to some contradictory conclusions and the evidence of the relationship of *AQP1* and PAH is still limited. However, n we describe two further families with PAH and variants in *AQP1*, expanding both the number of cases and the clinical associated phenotype. We provide further evidence of the association of *AQP1* and the development of hereditary and associated forms of PAH.

14h00 - SESSION 5: OVERGROWTH SYNDROMES (Chair: Damien Lederer)

14h00 - INVITED TALK, FRANCESC PALAU MARTINEZ: FUNCTIONAL GENOMICS FOR THE VALIDATION OF GENETIC VARIANTS IN NERODEVELOPMENTAL DISORDERS

14h45 - LUSCAN-LUMISH SYNDROME: EIGHT NEW CASES AND REVIEW OF THE LITERATURE

Presenting author: Alejandro Parra

Alejandro Parra^{1,2,3}, Jair Tenorio-Castaño^{1,2,3*}, Pedro Arias^{1,2,3}, Julián Nevado^{1,2,3}, Natalia Gallego^{1,2,3}, Fernando Santos-Simarro^{1,2,3}, Ignacio Arroyo⁴, Dr. Alfredo Santana⁵, Dra. Teresa Vendrell⁶, Dra. Mercedes Artigas⁷, Gabriel Martos⁸, The SOGRI Consortium^{1,2,3}, Pablo Lapunzina^{1,2,3}.

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Luscan-Lumish syndrome (LLS) is a relative recent overgrowth disorder. Clinical features of patients with LLS also included neurodevelopmental disorders such as intellectual disability, autistic behavior and epilepsy. Since the initial description, only few cases have been reported in the literature, with the lack of deep phenotyping and molecular underlying mechanism. LLS is caused by pathogenic variants in SETD2, which encoded a methyltransferase protein involved in histone regulation, playing an important role in gene expression.

Here, we report nine additional individuals with LLS, in which pathogenic or likely pathogenic variants were detected by the analysis of a custom NGS panel (214 genes), from a cohort of >2000 cases with overgrowth disorders.

Most common clinical features of the patients included overgrowth, intellectual disability, and neurodevelopmental disorders with variable degree of severity. We have also seen that autism behaviour is quite common, and can appear without overgrowth. At molecular level, we have detected nine new variants not reported previously in the literature, expanding the causative variants in LLS. The majority of the variants detected were nonsense and frameshift, which is in line with low tolerance of SETD2 for this kind of changes according to the pLI score (pLI=1). In summary, we report nine additional cases with LLS and reviewed clinical and molecular features of all cases described.

15h00 - FAMILIAL CASES WITH GPC3 MUTATIONS FROM LITHUANIAN COHORT WITH OVERGROWTH SYNDROMES

Presenting author: Aušra Matulevičienė

Beata Aleksiūnienė¹, Natalija Krasovskaja¹, Eglė Benušienė², Karolis Baronas¹, Kristina Grigalionienė¹, Raimonda .Meškienė¹, Algirdas Utkus¹, <u>Aušra Matulevičienė¹</u>

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Simpson–Golabi–Behmel syndrome (SGBS) is a rare X-linked congenital malformation syndrome. It belongs to a group of overgrowth syndromes (OGs) and is associated with high neoplasia risk. The characteristic features mostly present in males during pre- and postnatal periods and include overgrowth (polyhydramnios, organomegaly), distinctive craniofacial features (macrocephaly with coarse face, hypertelorism, macrostomia, macroglossia), abdominal organomegaly (hepatosplenomegaly) and intellectual disability. This syndrome is caused by loss-of-function mutations in *GPC3* gene.

Here, we present patients with SGBS from three non-related non-consaquineous families. They had characteristic phenotype, with features presenting from the second trimester of pregnancy. One of the children died at age of 2 months due to cardiopulmonary insufficiency and progressive hepatosplenomegaly.







With standard molecular genetic techniques like Sanger sequencing, RT-PCR and MLPA, we identified the following mutations in *GPC3* gene: Sanger sequencing from amniotic fluid revealed hemizygous pathogenic variant NM_004484.3:c.1159C>T,

(NP_004475.1:p.(Arg387Ter) in exon 4 in patient 1; exon 5-8 deletion of the *GPC3* gene in patient 2; deletion of exon 3: NM_004484.3:c.(474_574)_(1054_1253)del in patient 3. All females carriers from this cohort had SGBS features, including macrostomia, macrosomia, hypertelorism and macrocephaly.

The analysis of identified *GPC3* mutations related to OGs will help to develop and implement personalised follow-up plans for these patients, in particular, to facilitate prevention and optimize healthcare strategy for neoplasia.

Grants: This study is a part of the GOSPL (No. S-LL-21-5) project, which have received funding from the Research Council of Lithuania (RCL).

15h15 - TWO SPANISH PATIENTS WITH CTNNB1-RELATED SYNDROME

Presenting author: Laura Trujillano

Trujillano L, Lasa-Aranzasti A, Valenzuela I, Cueto-Gonzalez A, García-Arumí E, Tizzano E.

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Introduction: *CTNNB1*-related syndrome (OMIM # 615075) is an autosomal dominant neurodevelopmental disorder characterized by a variable degree of cognitive and language impairment, microcephaly, ophthalmologic findings consistent with exudative vitreoretinopathy, refractive errors and strabismus, truncal hypotonia, peripheral spasticity and dysmorphic features. Less common features include intrauterine growth restriction, feeding difficulties, and scoliosis. Here we report two further patients from two unrelated families with *CTNNB1*- related syndrome.

Material and Methods: In the two presented cases, the common clinical features included global developmental delay, absent speech, spastic diplegia, ophthalmological involvement and some dysmorphic features such as microcephaly,

strabismus, full nasal tip, long philtrum, thin upper lip, fair skin, arched and sparse eyebrows and hooded upper eyelid. Due to overlapping phenotype with Angelman syndrome, MS-MLPA analysis was initially performed and resulted negative in both cases. Then, whole exome sequencing (WES) was analyzed including *CTNNB1* (MIM* 116806) as a candidate gene.

Results: In the first patient WES identified a pathogenic variant [NM_001904.3:c.881T>A/p.L294*] in *CTNNB1* gene. In the second case, the copy number variant (CNV) analysis detected an heterozygous deletion [NM_001904.3:c.(936+1_937-1)_(*1106_?)del] involving







at least exon 7 to the end of the *CTNNB1* gene classified as probably pathogenic. Both identified variants were *de novo in* our patients.

Conclusions: *CTNNB1* gene must be considered in the differential diagnosis of Angelman syndrome. We suggest that *CTNNB1*- related syndrome is a recognizable entity given the shared dysmorphias among the patients. In the same line, we would like to conclude by emphasizing that a dysmorphology assessment and a detailed physical examination is a fundamental guide to the diagnosis of *CTNNB1* patients.

15h30 - FGFR2 AND OVERGROWTH: CLASSIC GENE, UNUSUAL PHENOTYPE

Presenting author: Alessandro Mauro Spinelli

Alessandro Mauro SPINELLI ^{1#}, Carla PITTINI ², Giulia PARMEGGIANI ³, Stefania ZAMPIERI ¹

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Case report: a 8-month-old girl, the second child of unrelated healthy Caucasian parents, was initially evaluated for megalencephaly (HC=+5,5 / +6 SD with slight enlargement of lateral ventricles and subarachnoid spaces, normal developmental trajectory and no clinical sign of intracranial hypertension; HC=+3 SD at birth), somatic growth along high-normal channels (both weight and length=+2 SD, at birth=+2,5 / +3 SD); "cruzonoid" face since birth, normal bone age, slight diastasis of some skull sutures and no clinico-radiologic evidence of craniosynostosis or significant abnormalities of head shape.

Prenatal history: intermediate risk for trisomy 21 (NIPT was negative); fetal growth acceleration and mild polyhydramnios during the third trimester.

Family history was apparently non-contributory.

Clinical exome sequencing revealed a *de novo FGFR2* missense variant already reported in the medical literature (two sporadic cases, both with craniosynostosis and crouzonoid traits; in one case HC was +5,7 SD) and absent in population databases, located between the second tyrosine kinase domain (TK2) and the interkinase region of the receptor, very far from the "classic" mutational clusters.

aCGH and karyotype analysis on peripheral blood were normal.

Head circumference peaked at +8 SD during follow-up visits.

Conclusion: while it is not new that *FGFR2*-related disorders may show CNS involvement suggestive of primary PI3K/AKT/mTOR overactivation (Semin Perinatol. 2015 Feb;39(1):36–43) our findings raise the question if an underlying genotype-phenotype correlation with megalencephaly can be established for this variant and possibly for other variants in







"atypical" regions of the gene. Definite correlations and mechanisms could lead to therapeutic trials of known pathway inhibitors.

15h42 - WHEN THE CLINICAL FOLLOW UP ADDRESSES THE DIAGNOSIS: RASA1 AND CM/AVM, A CASE REPORT

Presenting author: Maria Francesca Bedeschi

Martina RIMOLDI¹, <u>Roberta VILLA¹</u>, Maria IASCONE², Silvana GANGI³, Matteo PORRO⁴, Alessandro DRAGHI¹, Laura BASSI³, Maria Francesca BEDESCHI¹

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This case report describes a 4 year-old boy which was referred to genetic evaluation at birth due to a prenatal history of severe polyhydramnios with fetal macrosomia, born large for gestational age and with macrocephaly. Brain MRI, performed at birth, revealed a slight herniation of the cerebellar tonsils (suggestive for Chiari type 1 malformation), a dysmorphic corpus callosum and lateral ventricles.

Due to the neonatal presentation we suspected an overgrowth syndrome and we performed a target-NGS panel including *CDKN1C*, *DIS3L2*, *GPC3*, *NSD1*, *NFIX*, *OFD1*, *EZH2*, *PTEN*, *IGF2* -and MLPA of the *PTEN* gene, which turned out both negative.

During the clinical follow up, an eruptive angiomatosis, referable to capillary malformation—arteriovenous malformation (CM/AVM), and two cafè-au-lait spots on the upper limbs emerged. Subsequently the boy underwent WES-trio analysis which revealed the presence of a likely pathogenic heterozygous variant c.693-5A>G in the *RASA1* gene, maternally inherited. Reverse phenotyping in the mother revealed the presence of several cutaneous abnormalities compatible with CM/AVM.

No other pathogenic or likely pathogenic variants in genes related to macrocephaly were detected.

Monoallelic variants in the *RASA1* gene are associated to an autosomal dominant clinical condition called "Capillary Malformation-Arteriovenous malformations" (CM–AVM; MIM #608354) syndrome, which characteristically presents with multifocal small CM preferentially localized on trunk, face and limbs and AVMs, fast-flow anomalies that are common in the central nervous system but also occur in skin and other organs. Additional-findings observed in individuals with-*RASA1*-CM-AVM syndrome include lymphatic malformations and hydrocephalus.

With our case report we want to highlight the role of the clinical follow up in order to reveal additional signs/symptoms, support the diagnostic process and enhance WES data interpretation: if trio-WES had been performed in the neonatal period, it would have been







likely not informative due to the lack of pathognomonic vascular malformations at birth. This is especially true for genetic conditions in which the appearance of clinical features may be age-related.

Moreover we stress the possible neonatal presentation of *RASA1*-CM-AVM syndrome₂- as the presence of macrocephaly and overgrowth was not so frequently reported in association with *RASA1* at the time of clinical referral.

15h54 - A FURTHER CASE OF *POLR2A*-RELATED SYNDROME WITH HYPOTONIA, DEVELOPMENTAL DELAY AND ADDITIONAL FEATURES

Presenting author: Álvaro Martín-Rodríguez

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POLR2A gene encodes RBP1, the largest subunit of the RNA polymerase II complex (pol II). Pathogenic variants in *POLR2A* have been recently associated with a neurodevelopmental syndrome comprising hypotonia, a variable degree of developmental delay/intellectual disability, seizures and failure to thrive or feeding difficulties.

We present a novel case of *POLR2A* syndrome (MIM #618603), a 6-year-old girl presenting with a history of neonatal hypotonia, developmental delay, learning difficulties, failure to thrive, microcephaly and left hand preaxial polydactyly. In addition, an echocardiographic performed following her admission to due to apneas during the neonatal period revealed a dilatation of the ascending aorta. On examination, she showed some dysmorphic features (prominent forehead, epicanthal folds, strabismus and thin vermillion border of the upper lip) and brachydactyly. Brain MRI and EEG were both normal.

After several genetic tests, trio-whole exome sequencing identified a *de novo* missense variant in *POLR2A* (c.1400T>A; p.Met467Lys), not previously reported.

Our patient adds another case to this new POLR2A-related syndrome with some additional features not previously reported, thus contributing to the expansion of the associated phenotype.







16h45 - SESSION 6: SYNDROME DELINEATION, Neurology & central nervous system (Chair: Marije Meuwissen)

16h45 - PHIP-ASSOCIATED CHUNG-JANSEN SYNDROME: REPORT OF 22 NEW INDIVIDUALS

Presenting author: Alma Kuechler

Antje Kampmeier¹, Stefanie Beck-Wödl², Jasmin Beygo¹, Emilia K Bijlsma³, Nuria C Bramswig¹, Christel Depienne¹, Miriam Elbracht⁴, Ute Grasshoff², Tobias B Haack², Maria Haanpää⁵, Uwe Heinrich⁶, Rami Abou Jamra⁷, Margarete Koch-Hogrebe⁸, Hannele Koillinen⁵, Eva Lausberg⁴, Elsa Leitão¹, Vanesa López-González⁹, Catarina Macedo¹⁰, Ilaria Parenti¹, Denny Popp⁷, Imma Rost⁶, Kevin Rostasy⁸, Claudia Ruivenkamp³, María José Sanchez-Soler⁹, Ariane Schmetz¹¹, Carmen Steinborn¹², Sabine Weidensee¹³, Dagmar Wieczorek¹¹, Frank J Kaiser^{1,14}, Alma Kuechler¹

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At the "Bischenberg Meeting" 2021, we originally presented four patients with PHIP-associated Chung-Jansen syndrome (CHUJANS, OMIM #617991). This was the beginning of an international collaboration by which clinical and genetic data of 22 new patients with CHUJANS were collected that we are going to present at this year's meeting. CHUJANS is mainly characterized by developmental delay (DD), learning difficulties/intellectual disability (ID), behavioral abnormalities, facial dysmorphism and obesity. It is caused by haploinsufficiency of *PHIP* (pleckstrin homology domain interacting protein, OMIM *612870). While single base pair substitutions resulting in exchanges of specific amino acid residues or a premature stop of translation were identified by whole exome sequencing, larger deletions affecting parts of *PHIP* or span the entire gene as well as adjacent genomic regions were detected by different types of array analyses. Segregation analyses showed







either *de novo* occurrence or inheritance from an also (mildly) affected parent. In accordance with previously described patients, almost all individuals reported here show developmental delay (20/22), learning disability or ID (21/22), behavioral abnormalities (18/22), weight problems with increasing age (15/22) and characteristic craniofacial features (esp. prominent eyebrows, thick alae nasi, and long philtrum (22/22)). Our findings further expand the mutational and clinical spectrum of *PHIP* and CHUJANS. We discuss the molecular and clinical features in comparison to the published individuals. The fact that some variants were inherited from a more mildly affected parent further illustrates the variability of the associated phenotype and underscores the importance of a thorough clinical evaluation combined with genetic analyses for accurate diagnosis and counselling.

17h00 - TWO DISTINCT PHENOTYPES IN PATIENTS WITH RHEB-RELATED MTOR-PATHY - WHETHER THE LOCALIZATION OF VARIANTS IN SWITCH DOMAINS OF RHEB PROTEIN MATTERS?

Presenting abstract: Malgorzata Pawlowicz

Malgorzata Pawlowicz 1,2), Malgorzata Rydzanicz3), Piotr Stawinski3), Rafal Ploski3)

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Objective: Three published cases of *RHEB*-related disorders are associated with missense variants located in regions encoding Switch I/II domains in RHEB protein (Reijnders 2017). We present the fourth case of a 8-year-old boy of Polish origin carrying *de novo* heterozygous missense variant c.100T>C (p.Ser40Pro) in the *RHEB* gene in comparison to the previously published phenotypes grouped according to their association with Switch I or II domain of RHEB protein.

Methods: The presented patient was qualified for the WES analysis under the program of cerebral palsy re-diagnosis in the Warmia-Mazury Region (North Poland) in 2019-2021. WES analysis was performed using Illumina platform and verified by Sanger sequencing. Analysis of variant segregation in family confirmed *de novo* status of *RHEB* variant identified in proband. Classic syndromes associated with clinical signs observed in patient and caused by chromosomal rearrangements were excluded. Patient's phenotype was compared to the published cases (Reijnders 2017), taking into account the functional division into cases caused by changes located in the Switch I (group 1) or Switch II domain (group 2) of RHEB protein.

Results: The presented patient, together with two published patients, was placed in the group 1 and the third published patient in the group 2. Phenotype observed in the group 1 was more complex and severe with exclusive occurrence of dynamic muscles tone evolution from generalized hypotonia to spastic tetraparesis, neuromuscular scoliosis, hip dislocation, gastro-oesophageal reflux, episodes of hyperventilation and heart arrhythmias. Seizures







occurred in patients in both groups with diffuse EEG epileptic abnormalities (including hypsarrhythmia) and some drug resistance in group 1. Patients in both groups had similar dysmorphic features: a round face with a triangular chin, discreet hypertelorism, deeper setting eyeballs, a wide bridge of nose, and a narrow upper lip. In the presented patient, progressive prognathic features were observed with age, as in other patients from the group 1.

Conclusions: RHEB-related disorders could be considered a new mTOR-pathy in which the localization of the variant in a specific Switch domain in the RHEB protein determines the severity of clinical presentation and the scope of therapeutic management.

Keywords: RHEB gene, Switch domains, mTOR pathway

		Switch I domain		Switch II domain
	(position 34-40)			(position 64-80)
	Patient 1 (this report)	Patient 2 (Reijnders et al. 2017)	Patient 3 (Reinders et al. 2017)	Patient 4 (Reijnders et al. 2017)
RHEB variant	5.50 0 5555			
cDNA position	c.100T>C	c.110C/T	c.110C>T	c.202T>C
protein position	p.Ser34Pro	p.Pro37Leu	p.Pro37Leu	p.Ser68Pro
chromosome position (Hg38)	Chr7:151490967A>G	Chr7: 151490957G>A	Chr7: 151490957G>A	Chr7:151477406A>G
Development evaluation				
motor skills	not sitting	supported walking (20 mo)	sitting (18 mo)	standing with support
	not walking	unsupported walking (4 yr)	walking (13 yr)	
expressive speech skills	babbling	minimal non-verbal communication	using a few words	no expressive speech
intellectual disability	profound	severe-profound	severe	severe-profound
Neuromuscular signs (RHEB p	rotein expression: medium – ce	rebral cortex, low – basal gangli	a, hippocampus and cerebellun	1)
muscles tone dynamics				
(generalized hypotonia >				
spastic tetra- paresis/plegia)				
neuromuscular scoliosis/kyphoscoliosis			*	
hip dislocation	+	+	+	
	(6 yr)	(5 yr)	(congenital)	
episodes of hyperventilation	+	+	+	
seizures		0		*
(age of onset)	(16 mo)		(3 yr)	(NA)
<u></u>	diffuse hypofunctional abnormalities			
		diffuse hypofunctional	diffuse epileptiform	localized epileptiform
EEG abnormalities	progression of epileptiform abnormalities from localized	abnormalities	abnormalties	activity
	to diffuse	(mainly occipital lobes)	(mainly right frontal lobe)	(right temporal lobe)
	(mainly central and parietal regions)			
Gastrointestinal signs (RHEB p	rotein expression: medium – es	ophagus, stomach, duodenum,	small intestine, colon, rectum,	liver, gallbladder)
gastro-oesophageal reflux	+	+		

17h12 - A HOMOZYGOUS NONSENSE VARIANT IN LAMA1 ASSOCIATED WITH PORETTI-BOLTSHAUSER SYNDROME: A CONSANGUINEOUS CASE REPORT

Presenting author: Teresa Carrión Mera

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Background/Objectives: A 6-year-old girl diagnosed with Arnold-Chiari malformation comes to our genetic consultation due to a repaired occipital encephalocele and multiple MRI abnormalities including periventricular and ependymary heterotopias, cerebellous cortical dysplasia and corpus callosum hypoplasia. Other symptoms are epilepsy, psychomotor







delayed, gynecomastia, precocious puberty, ophthalmologic abnormalities (bilateral optic neuropathy, strabismus, and nystagmus) and several facial dysmorphisms (epicanthus, broad eyebrows and synophrydia. The patient was born of consanguineous parents at 38+5 gestation weeks by cesarean due to a prenatally detected neural tube defect.

Methods: Karyotype and CGH array were performed. Clinical exome was sequenced by Human Whole-Genome Sequencing with the NexteraTM DNA Flex Library Preparation Kit (Illumina).

Results: Karyotype and CGH array were normal. The analysis of the clinical exome showed a homozygous autosomal recessive (AR) nonsense variant c.842G>A (p.Trp281X) in *LAMA1* (NM 005559.4), classified according the ACMG guidelines as pathogenic.

Conclusion: LAMA1 encodes the Laminin alpha-1 protein required for the basement membranes and thus is critical in early embryonic development (Cai et al, 2021). Homozygous or compound heterozygous mutations in LAMA1 are associated with Poretti-Boltshauser syndrome (PTBHS) (OMIM #615960), a rare AR disorder characterized by a non-progressive cerebellar ataxia (cerebellar dysplasia, cerebellar vermis hypoplasia), delayed motor development and speech delay. The cognitive function can range from normal to intellectually disabled. Additional ophthalmological phenotypes such as high myopia, variable retinal dystrophy, and eye movement abnormalities are also associated with this condition (Aldinger et al, 2014). This condition should not be confused with Joubert syndrome since it has a much more limited phenotype (Powell et al, 2021).

References: 1. Cai, Cindy X et al. "OCULAR MANIFESTATIONS OF PORETTI-BOLTSHAUSER SYNDROME: FINDINGS FROM MULTIMODAL IMAGING AND ELECTROPHYSIOLOGY." Retinal cases & brief reports, 17 Mar. 2020; 2. Aldinger, Kimberly A et al. "Mutations in LAMA1 cause cerebellar dysplasia and cysts with and without retinal dystrophy." American journal of human genetics vol. 95,2 (2014): 227-34; 3. Powell, Laura et al. "Identification of LAMA1 mutations ends diagnostic odyssey and has prognostic implications for patients with presumed Joubert syndrome." Brain communications vol. 3,3 fcab163. 16 Jul. 2021

17h24 - A SEVERE CASE OF NEONATAL ENCEPHALOPATHY ASSOCIATED WITH *TAF1C* VARIANTS

Presenting author: Louise Goujon

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Introduction: *TAF1C* gene encodes for the TATA box binding protein associated factor 1 C (TAF1C), a subunit of the TBP-TAF complex Selectivity Factor 1 (SL1) (1). SL1, such as the







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upstream binding transcription factor (UBTF), belongs to the RNA polymerase I (Pol I) transcription machinery, which is implicated in the synthesis of ribosomal RNA (2). The dysregulation of ribosome biogenesis has already been linked to different human diseases (3). Some genes related to the Pol I machinery, notably *UBTF*, have been associated with neurological human impairment (4)(5)(6). More recently, homozygous variants in the *TAF1C* gene were reported in two unrelated patients with a severe childhood onset neurological phenotype (7).

Case Report: Here we report a new patient with compound heterozygous variants in *TAF1C* gene. Antenal history was marked by an hydramnios and fetal hypomobility. Neonatal presentation included hypotonia, seizures, hypospadias and cryptorchidism. Electroencephalogram showed a pathological pattern and brain MRI showed a short corpus callosum. Exome sequencing identified two variants in *TAF1C*, respectively inherited from each parent. The first likely pathogenic variant has previously been described by Knuutinen et al in a homozygous state in a patient with neurodevelopmental delay and epilepsy (7). The other variant was absent from different databases in a homozygous state and was predicted to be pathogenic by the in silico predictive software tools. The newborn child died at the age of one month of life.

Conclusion: This case of severe neonatal encephalopathy contributes to consider *TAF1C* as a potential cause of recessive early onset neurological disorder and expands the neurologic phenotype associated with *TAF1C* variants.

References: 1. Di Pietro C, Rapisarda A, Amico V, Bonaiuto C, Viola A, Scalia M, et al. Genomic localization of the human genes TAF1A, TAF1B and TAF1C, encoding TAF148, TAF163 and TAFI110 subunits of class I general transcription initiation factor SL1. Cytogenet Genome Res. 2000;89(12):133 6. 2. Russell J, Zomerdijk JCBM. The RNA polymerase I transcription machinery. Roberts SGE, Weinzierl ROJ, White RJ, éditeurs. Biochem Soc Symp. 1 janv 2006;73:203 16. 3. Hannan KM, Sanij E, Rothblum LI, Hannan RD, Pearson RB. Dysregulation of RNA polymerase I transcription during disease. Biochim Biophys Acta BBA - Gene Regul Mech. mars 2013;1829(3 4):342 60. 4. Toro C, Hori RT, Malicdan MCV, Tifft CJ, Goldstein A, Gahl WA, et al. A recurrent de novo missense mutation in UBTF causes developmental neuroregression. Hum Mol Genet. 15 févr 2018;27(4):691 705. 5. Bastos F, Quinodoz M, Addor MC, Royer-Bertrand B, Fodstad H, Rivolta C, et al. Childhood neurodegeneration associated with a specific UBTF variant: a new case report and review of the literature. BMC Neurol. déc 2020;20(1):17. 6. Ikeda C, Kawarai T, Setoyama C, Orlacchio A, Imamura H. Recurrent de novo missense variant E210K in UBTF causes juvenile dystonia-parkinsonism. Neurol Sci. mars 2021;42(3):1217 9. 7. Knuutinen O, Pyle A, Suo-Palosaari M, Duff J, Froukh T, Lehesjoki AE, et al. Homozygous TAF1C variants are associated with a novel childhoodonset neurological phenotype. Clin Genet. nov 2020;98(5):493 8.







17h36 – EBF3-RELATED SYNDROME: A RECOGNIZABLE CONGENITAL PEDIATRIC ATAXIA

Presenting author: Claudia Ciaccio

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EBF3 is a gene located in the 10q26.3 chromosomal region whose aploinsufficiency causes a syndrome characterized by intellectual disability, possible additional neurodevelopmental disorder (mostly ADHD, Autism Spectrum Disorder, non-specific behavioral problems), hypotonia, and ataxia, this letter present despite in most patients brain MRI is reported to be normal. Strabismus, congenital malformations of the genitourinary, gastrointestinal, or musculoskeletal system, and shared facial dysmorphisms (long face, tall forehead, high nasal bridge, deep philtrum, straight eyebrows, short and broad chin, mildly dysmorphic ears) are also reported.

We describe a cohort of 6 children, 4 with a EBF3 mutation and 2 with a 10q26 deletion; they are 2 females and 4 males, aged between 2 and 12 years. Clinical evaluation was performed by a pediatric neurologist and pediatric dysmorphologist; ataxia severity was rated by SARA; all brain MRI were reviewed by expert radiologists; and the GQ level was obtained through standardized Griffiths Mental Development Scales. The 6 children globally present the same phenotype, but with significative differences in severity expression of the disease.

3 of the 4 children with a EBF3 mutation carry a missense variant, one child has a novel frameshift variant, and the other 2 carry a similar 10q26.2q26.3 loss. Developmental milestones were delayed in all patients and result in variable cognitive outcomes (2 with moderate and two with mild impairment, the 2 deleted patients have normal GQ scores); none of them have a definite diagnosis of other neuropsychological issues, but share some behavioral disturbs, in particular attention deficit or low frustration tolerance. They all show signs of cerebellar involvement, confirmed by SARA scores; strabismus and dyspraxic oculomotor functions are present in 6/6 children; orobuccal dyspraxia and/or dysarthria is recurrent. Hypotonia is common while tremor and/or dysmetria is noted in 5/6 patients and ataxic gait is present in all children (SARA score range 9 to 20 out of 40 points). Brain MRI reveals in all children a peculiar cerebellar malformation with foliation anomaly and vermis hypoplasia; patients with EBF3 mutations present a recognizable radial disposition of cerebellar folia, that in sagittal MRI takes on a dandelion appearance (dandelion sign). Most children have common facial traits (mostly deep set eye and thin upper lip) and a growth







below -2SD, with all of them showing a height below the mean value. Some minor malformations can be presents, and stipsis is reported in half of our patients but all children globally have good general health.

All together, the neurological and neuroradiological presentation and some of the dysmorphic and malformative traits make EBF3-related syndrome quite a recognizable condition: we underline here the features that could lead to diagnosis or be important elements of the back phenotyping process derived from big-data analyses.



17h48 - *PRMT7* mutations as an important differential diagnosis to Albright hereditary osteodystrophy

Presenting author: Anneke T. Vulto-van Silfhout

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Introduction: Since the introduction of exome and genome sequencing the diagnostic yield in patients with intellectual disability and congenital anomalies has greatly increased. However, the underlying cause can still not be identified in a significant number of patients.

Case report: A 13 year old girl presented for the third time to our clinical genetics department. She was born with a single umbilical artery. She had developmental delay. Neuropsychological testing showed a disharmonic IQ (VIQ 60, PIQ <55). Since the age of 18 months she had myoclonic astatic epilepsy (Doose syndrome) which was refractory to







medication. She suffered from recurrent urinary tract infections. Physical examination showed a length of 147,8 cm (-2 SD), weight of 52 kg (+2,3 SD) and head circumference of 52 cm (-1,4 SD). Facial dysmorphisms consisted of a high forehead, upslanted palpebral fissures, upturned nasal tip with full alae nasi, long philtrum, cupid's bow shaped upper lip, two missing teeth. Her hands showed broad thumbs, tapering fingers, short 4th and 5th metacarpals. She also had broad halluces valgus. Extensive previous genetic testing was performed, including trio exome sequencing, targeted analysis of *SLC2A1*, *SCN1A* and *GNAS1*, SNP array and metabolic screening, which were all normal.

Results:_Repeat exome sequencing analysis now showed compound heterozygous mutations in *PRMT7*. Recessive *PRMT7* mutations have been described in 15 patients thusfar with a phenotype of short stature, brachydactyly, impaired intellectual development and seizures (SBIDDS, MIM #617157). The phenotype can be considered a phenocopy of Albright hereditary osteodystrophy (AHO, pseudohypoparathyroidism) and is highly similar to the phenotype in our patient. AHO is caused by loss-of-function mutations of the *GNAS* gene on the maternal allele, which was previously investigated in our patient. PRMT7 is member of the protein arginine methyltransferase family with an important role in cellular regulatory pathways. The link between PRMT7 and GNAS is currently unclear and requires further study.

Conclusion: Mutations in *PRMT7* are an important differential diagnosis in a patient with a clinical suspicion of Albright hereditary osteodystrophy. This report also shows the value of reanalysis of exome sequencing data in cases where a diagnosis could not be established previously.

18h00 - GENETIC COMPLEXITY IN OCULOCUTANEOUS ALBINISM TYPE 1 IN ONE FAMILY

Presenting author: Kai Muru

<u>Kai Muru</u> ^{1,2}, Laura Mauring ^{1,3}, Rael Laugesaar ^{2,4}, Hanno Roomere ¹, Ülle Murumets ¹, Sander Pajusalu ^{1,2}

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Albinism is a group of hereditary conditions characterized by decreased or absent ocular pigmentation and variable skin and hair pigmentation. It can be divided into oculocutaneous albinism, ocular albinism and syndromic albinism. Skin, hair and eye hypopigmentation is variable in albinism, and clinical and genetic heterogeneity of the disease prevents establishing phenotype-genotype correlation.

Ocular albinism type 1 (OCA1) is associated with *TYR* variants and it is the most common subtype of autosomal-recessive oculocutaneous albinism found in Caucasians. Pathogenic variants in *TYR* cause complete or partial form of OCA1. Hypomorphic variants (Arg402Gln and Ser192Tyr) of *TYR* have been reported as polymorphisms before, but recent publications







have shown that the hypomorphic variants act as pathogenic variants when they are present in *trans* and inherited with a deleterious *TYR* variant.

Case report: The proband is a second child in family. At the age of 2 months, nystagmus was first noticed. At the age of 2 years hypopigmentation of the skin and hair, and distinct ocular changes were described. Her sister has also hypopigmentation of the skin and hair, but she does not have ocular changes. Mother and father do not have hypopigmentation of the skin or hair and no ocular signs. Father has two brothers; the younger brother has hypopigmentation of the skin and hair and marked photophobia, but no typical ocular findings. Proband father's parents do not have characteristic clinical symptoms to OCA1.

NGS panel analysis (TruSight One Expanded panel, Illumina) in proband revealed in *TYR* (NM_000372.4) gene two pathogenic variants *in trans*: c.650G>A p.(Arg217Gln) inherited from the mother and c.1217C>T p.(Pro406Leu) inherited from the father, and heterozygous hypomorphic variant c.1205G>A p.(Arg402Gln). NGS panel in father's brother revealed in *TYR* gene heterozygous pathogenic variant c.1217C>T p.(Pro406Leu) and *in trans* heterozygous hypomorphic variant c.1205G>A p.(Arg402Gln). They did not carry the other hypomorphic variant c.575C>A p.(Ser192Tyr). Addition analysis in this family revealed in proband's father the same genotype with his brother (Pro406Leu/Arg402Gln); the proband's sister and mother has in *TYR* gene following variants: in one allele pathogenic variant Arg217Gln and additionally homozygous hypomorphic variant Arg402Gln.

Conclusion: We report a family where one of the members presents with typical OCA1 caused by biallelic pathogenic variants in *TYR*. Surprisingly, classical phenotype of OCA1 was not present in the family with biallelic variant including one pathogenic variant and one hypomorphic variant *in trans*. Variability in OCA1 phenotype-genotype shows need for molecular testing for proper patient management and as well for correct genetic counselling.

20h00 - UNKNOWN SESSION (Chair: Alain Verloes)

20h00 - A MORE UNIQUE THAN RARE FETUS PRESENTING TRIGONOCEPHALY, DYSMORPHISMS AND MONOLATERAL AGENESIS OF FIFTH HAND RAY

Presenting Author: Agnese Feresin

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We report a fetus with trigonocephaly, dysmorphisms and monolateral agenesis of fifth hand ray within a likely syndromic presentation. It was the first pregnancy of an unrelated, healthy couple of Caucasic ancestry, with a maternal and paternal age of 33 and 49, respectively. At the family history, a maternal grandfather is reported to have isolated six hand fingers.

The pregnancy was spontaneous and no gestational diabetes was detected. After a normal ultrasound examination (US) and low risk screening at first trimester, an increased fetal growth (>95° percentile) emerged at the second trimester US screening, without visceral malformations and with a normal amount of amniotic fluid. At the 3rd trimester US screening at 33 weeks of amenorrhea, the absence of the 5th finger of left hand was suspected and then confirmed by our Prenatal Diagnosis Center, which also showed a trigonocephaly and an incremented amount of amniotic fluid. CT confirmed the synostosis of metopic suture and the presence of four rays of left hand. Biochemical analysis and the dosage of alfa-feto protein in amniotic fluid were performed and microarray analysis of fetal DNA excluded genomic imbalances. The couple required the termination of pregnancy, performed at 34,6 weeks of amenorrhea, in accordance with French law. A fetal post-mortem examination was performed at the referral fetopathology unit. The male fetus appeared macrosomic with an advanced bone biometry and a delayed bone maturation compared to the gestational age. A trigonocephaly due to a complete closure of metopic suture was objectified together with some facial dysmorphisms including upslanted palpebral fissures, hypotelorism, epicanthus, small nose with large nares and short philtrum. A complete agenesis of the left 5th ray of the left hand was confirmed, with normal right hand and reducible club-foot. The fetus also presented thin and shortened ribs. Visceral examination reported the presence of an accessory spleen, a dilated gallbladder with an anatomic variation of coronaries position. No histological anomalies was found in organs and placenta.

The comprehensive clinical presentation of the fetus is unusual. 5th ray agenesis is exceptional. In Human Phenotype Ontology "postaxial oligodactyly (HP:0006210)" is the only term proposed in the field and it has been rarely reported in hand or hands/foot isolated presentations such as Ulnar/fibula Ray Defect-brachydactyly Syndrome and Tetramelic Postaxial Oligodactyly, without known gene associations. However, trigonocephaly with other postaxial hand anomalies, such as polydactyly with or without a concurrent preaxial involvement are related to Greig cephalopolysyndactyly syndrome related to *GLI3* alterations. Craniosynostosis are more frequently associated with preaxial limb malformations concerning the radial ray, as in Baller-Gerold syndrome.

Exome sequencing is currently performed to unravel the genetic cause of this polymalformative syndrome.







20h10 - UNDIAGNOSED CASE OF DYSMORPHIC FACIAL FEATURES AND GLOBAL DEVELOPMENTAL DELAY

Presenting author: Ana Isabel Sánchez

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Past medical history:

Perinatal: controlled pregnancy without incidents. Hospital delivery at term (37+5). Apgar 8/9/10, pH 7.37, BW: 2600 (p13), L: 46 cm (p4), HC: 33 c m (p31) CMV was detected in urine due to peculiar phenotype (negative, discharged). No resuscitation or neonatal admission was required. No documented jaundice or hypoglycemia. No feeding difficulties, metabolic screening performed in Madrid was normal.

Psychomotor development: global neurodevelopmental delay.

Bilateral congenital cataract.

Family history: First child from non-consanguineous parents.

No family history of developmental delay, intellectual disability, autism spectrum disorder o genetic syndrome.

Physical examination: Head circumference: 46.5 cm (microcephaly). Height and height in10th percentile. Sparse and fine hair. Flat occiput. Narrow bitemporal diameter, prominence of the metopic suture. Superiorly oriented palpebral fissures, hypotelorism. Infra-orbital fold. Bilateral congenital cataracts. Very high arched eyebrows with fine and sparse hair, synofris. Slight malar flattening (mid face hypoplasia). Flattened long philtrum, cupid-bow upper lip.

Anteverted nares. Small tip of nose. Triangular mouth. Intact and high palate. Well set ears and posteriorly rotated, with prominent antihelix.

Clinodactyly and shortening of the 5th finger of both hands. Square palms. Plantar arches present. Retractile testicles, palpation of the right testicle in the inguinal canal is easier than the left one. No café-au-lait spots or other skin lesions. Angioma in the scalp.

Genetic studies performed: Karyotyping in peripheral blood, array CGH in peripheral blood and oral tissue with no pathogenic or likely pathogenic copy number variations.

Clinical exome: no pathogenic, likely pathogenic or VUS variants.

Undiagnosed case.







20h20 - AN UNDIAGNOSED PATIENT WITH INTELLECTUAL DISABILITY, BRAIN ABNORMALITIES AND DYSMORPHIC FACIES

Presenting author: Ana Miguel Capela

Ana Miguel CAPELA 1, Cláudia FALCÃO REIS 1

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We report the case of a 13 year old male, followed since infancy at our clinical genetics outpatient clinic due to developmental delays, macrocephaly and dysmorphic facial features.

He was born to a young non-consanguineous couple, a Portuguese mother with macrocephaly (59 cm +3,6 SDs) and Duane syndrome and a healthy Welsh father, with unremarkable family history. The pregnancy was inconspicuous, and he was delivered vaginally at 40 weeks with adequate APGAR score and anthropometry.

Concerns began at 6 months of age due to marked axial hypotonia, failure to thrive, and developmental delays. All marks of development were achieved late, with cervical control after 12 months and first spoken words after age 4 years. Brain MRI at ages 2yo and 6yo revealed hypoplasia of the corpus callosum, as well as unspecific findings.

Examination at 13-yo showed macrocephaly (59cm +3SDs), large forehead with high hair implantation, tented mouth, high palate, macrodontia, crowded teeth with open bite and low set and posteriorly rotated ears, short stature (<5th centile) and low weight (31 kgs -2,25 SDs), ataxia, strabismus, some behaviour problems with aggressive episodes, and poor speech (6 words). He is currently wheel-chair bound due to progressive scoliosis and complications of spinal surgery.

Throughout the years, extensive investigations were performed, with karyotype, *FMR1* expansion analysis, urinary guanidinoacetate and creatine-to-creatinine ratio, serum transferrin isoelectric focusing, urinary organic acids, serum and urinary aminoacids, serum very-long-chain fatty acids and phytanic acid levels, muscle biopsy, array-CGH and exome sequencing, all were unremarkable. FISH analysis of 12p in buccal swab sample is underway.

We welcome suggestions of a clinical or genetic diagnosis.













20h30 - A DIAGNOSIS THAT DOESN'T FIT? - SINGLE CASE REPORT

Presenting author: Raquel Gouveia Silva

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We describe a 10 years-old girl, the second daughter of healthy, non-consanguineous parents. From family history, we stand out, two paternal first cousins with intellectual disability (ID) and social interaction difficulties. Pregnancy was uneventful and the birth occurred at 38 weeks of gestation by cesarean delivery. Birth weight was 2840 g (5-10th centile), length 47 cm (10th centile), and head circumference 32 cm (5-10th centile). Apgar scores were 9/10. Since 4 months of age, parents noticed some visual difficulties. Ophthalmological examination, at this age, documented bilateral coloboma affecting the iris and retina, without involving the lens. She sat unsupported after eight months, transferred objects from one hand to the other at seven months, said her first single word at 18 months of age, walked alone at 26 months, and started to build sentences from 3 years of age. She evolved with chronic constipation and a mild to moderate ID, with asymmetrical and uncoordinated gait, poor fine motor skills and expressive language, and attention deficit disorder. She attended a personalized care program at school and benefited from speech therapy, and physiotherapy support to date.

She evolved with some dysmorphic features, namely: high forehead, large and detached ears, small and spaced teeth and micrognathia (Figure 1).

ArrayCGH (*Comparative Genomic Hybridisation, CGX-HD 180K, Signature Genomics, PerkinElmer*) was normal. Cerebral-MRI performed at 3 years, revealed abnormal cortical gyrus and brain atrophy. The echocardiogram and hip X-ray were both normal.

Solo whole exome sequencing (WES) was performed in 2018, revealing the presence of a heterozygous *de novo* missense, probably pathogenic variant in *FOXG1* gene (NM_005249.4): c.701C>G, p.(Ser234Cys).







Over time, she has evolved favorably at motor and language levels, without regression. When compared with other cases in the literature, our case presents with a milder clinical picture and a positive evolution. *FOXG1* Sanger sequencing was performed, confirming once more the presence of this variant. A higher phenotypic variability between *FOXG1* genotype groups has been described.

Besides the mild presentation, there still does not seem to be much consistency in which colobomas can be explained by variants in this gene, although the first steps in mice are trying to prove otherwise. Is this variant enough to justify the entire clinical picture? Suggestions on additional investigations or acquired knowledge, regarding *FOXG1* are welcome.



Figure 1 - Our patient at 3 y; 4 y; 6 y and 8 y (left to right)

20h40 - MALE WITH MULTIPLE MALFORMATIONS AND NO ETIOLOGICAL DIAGNOSIS

Presenting author: Celia Azevedo Soares

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A 13-month-old male infant was referred to our Medical Genetics consultation due to multiple malformations. He is the only son of a non-consanguineous couple, and was conceived by intracytoplasmic sperm injection. Gestation was complicated by maternal







cholestasis, 3rd-trimester restriction, and pre-eclampsia. He was born at the 33rd week of gestation with weight percentile (P) 6, length P14 and occipital-frontal circumference P39.5, normal newborn screening, but failed the neonatal hearing screening at the right side. His clinical features include short stature (P<1 -3.2SD), plagiocephaly, hypotonic triangular face with asymmetry, arched eyebrows, short palpebral fissures, grey sclera, unilateral epicanthus inversus, strabismus, anterior embryotoxon, bilateral nasolacrimal duct obstruction, bulbous nose, posteriorly rotated ears, pre-auricular pit on the right, deafness on the right ear, micrognathia, short neck, congenital muscular torticollis, vertebral fusion (C2-C3), umbilical and inguinal hernia, left ventricular hypertrabeculation, hypospadias, sacral dimple, and developmental delay. Normal abdominal and kidney ultrasound. Growth hormone therapy is being considered.

Karyotype was normal (46,XY). The investigation by 7-dehydrocholesterol, plasma amino acids, and urinary organic acids quantification, transferrin isoelectric point assay, and msMLPA for UDP7, showed no alterations. *Array*CGH identified a 1p12 duplication, inherited from a healthy parent, classified as a variant of unknown significance. WES singleton with no pathogenic findings. Similarity scores did not suggested a diagnosis that fit the clinical features.

Given the unsolved status of this case, the authors are open to suggestions of diagnosis or further investigation.

20h50 - UNKNOWN CASE WITH GLOBAL DEVELOPMENTAL DELAY, INTELLECTUAL DISABILITY AND DYSMORPHIC FEATURES FROM A CONSANGUINEOUS FAMILY

Presenting author: Hellen Lesmann

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Introduction: We report an 11-year-old girl with intellectual disability and dysmorphic features. She is the first of four children of consanguineous Egyptian parents and she has a similar affected brother.

Dysmorphic examination: After an uneventful pregnancy, she was born with a normal birth weight. In the course, however, she gained weight only with difficulty. Her weight is currently in the 3rd percentile. She shows several facial dysmorphic features such as thick arched eyebrows with synophrys, upslanting palpebral fissures and a staring gaze as well as a malar hypoplasia. She also has a scoliosis, a sandal gap, a clinodactyly of the 3rd fingers, an oligosyndactyly of the right foot and a hyperlaxity of interphalangeal joints. The younger brother shared similar clinical features.







Investigations: Imaging procedures such as echo and brain MRI showed normal findings. A normal result was obtained on the Auditory Brainstem Response Test. Intelligence testing revealed a verbal Intelligence Quotient (IQ) of 54 and a nonverbal IQ of 63. Computer-aided facial analysis using DeepGestalt and GestaltMatcher algorithm did not yield any suitable suggestions. Genetic testing, including chromosomal analysis and whole exome sequencing, showed no clear cause. With exome sequencing of both affected siblings and their parents, we identified a single candidate mutation in *LAMB4* which is in accordance with the segregation of the phenotype.

Conclusion: We report two similar affected siblings from a consanguineous family, who are highly suspicious for an autosomal recessive disorder.

21h00 - COULD COVID19 CAUSE HEMIFACIAL MICROSOMIA?

Presenting author: Jadranka Maksimovic

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Hemifacial microsomia (HFM), is a rare congenital malformation which could be caused by disruption of vascularization or by disruption of normal development of the 1st and 2nd branchial arches. Etiology is heterogenous from genetic defects, teratogens, drugs, substance uses, endocrinological disorders of and other factors such as different structural chromosomal abnormalities (partial duplication pregnant woman, microdeletion of 12p13, microdeletion of 22q11 etc.

Persons could have spectrum of different malformations with clinical continuum caused by disruption from mild to serious. Affected people could have different combination of anomalies that include unilateral craniofacial anomalies of maxilla, mandible, zygoma, muscles of mastication, trigeminal nerve, tragus, helical root, helix, malleolus, incus and antihelix, antitragus, and lobule and the hyoid bone, muscles of facial expression, facial nerve, stapes and eyes.

Here we present one 8-month-old girl with microtia, low settled left ear without external auditory canal and facial asymmetry. CT imaging showed that there is also disturbed normal anatomy of the left temporal bone and there is an asymmetry in the volume of the condyle of the mandible. Karyotype was normal. History showed that during early pregnancy, in 4th weeks of gestation mother suffered from COVID19.

Etiology of Hemifacial microsomia is heterogenous and COVID19 could be one of cause of Hemifacial microsomia but this statement needs further evaluation.







21h10 - A FAMILIAL SYNDROMIC INTELLECTUAL DISABILITY -AN INCONCLUSIVE CASE

Presenting author: Mariana Neves

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Case presentation: We describe a 16-year-old girl with a severe syndromic intellectual disability. She is the first child of a non-consanguineous couple and she was institutionalized in early childhood. The father was never present. The mother has similar but milder phenotype.

Personal history: During gestation polyhydramnios and shortened long bones were identified. She was born with 35 weeks of gestation and was hospitalized for 5 months in neonatal care unit due to respiratory distress, hypotonia, recurrent aspiration associated with laryngomalacia, craniofacial dysmorphisms and umbilical hernia. She evolved with global developmental delay and severe intellectual disability, microcephaly, divergent strabismus and nystagmus.

Dysmorphologic examination: The patient is mildly disproportionate due to long superior limbs. Her shoulders are anteriorly rotated with kyphosis posture, pectus excavatum and short neck. She presents a syndromic gestalt with an asymmetry long face, mild arched eyebrows and microretrognathia. It's observed bilateral cubitus valgus, abnormal digit morphology with bilateral fifth finger campodactly and bilateral transverse fold. She has bilateral pes cavus with the need of surgical correction. At neurological examination she presents lower limbs hypertonia and hyperreflexia with bilateral Babinski sign.

Investigations: Extensive investigation was performed with inconclusive results including negative metabolic investigation, normal CE-MRI and pituitary-MRI, muscular biopsy that demonstrated unspecific myopathic changes, normal OXPHOS study and normal CK. Genetic testing included a normal karyotype, negative arrayCGH (Affymetrix CytoScan 750K) and WES-duo (with the mother) with CNV analysis (Centogene AG).

Discussion and conclusion: We present a syndromic patient with inconclusive etiological investigation. She probably has an undiagnosed autosomal dominant syndromic intellectual disability with variable expressivity, inherited from the mother who has milder manifestations.







21h20 - AN UNKNOWN CASE OF 14-YEAR-OLD GIRL WITH PROFOUND INTELLECTUAL DISABILITY, STEREOTYPICAL MOVEMENTS AND EPILEPSY

Presenting author: Joanna Karwowska

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A 2-year-old girl was referred to genetic counselling unit due to developmental delay. She was born from the second pregnancy and first delivery by caesarean section in term with weight at 3280 g (25-50 centile), length 54 cm (>97 centile), head circumference 35 cm (75 centile) and 10 points in Apgar score with neonatal period complicated by prolonged newborn jaundice and axial hypotonia. At the age of 2 months the patient was diagnosed with bile ducts inflammation. Additional tests revealed single choroid plexus cyst and incomplete Hiss right bundle brunch block and normal EEG result.

Physical examination revealed delayed psychomotor development – she was not able to walk and tongued single syllables only. Dysmorphic features were not so evident: short nasal bridge and wide root, incomplete epicanthus, thick lower lip. She presented stereotypical hand movements (waving, kneading) and smiled frequently.

At the age of 3 years and 3 months she was able to stand up holding on to furniture, walk by the hand and babble. She presented fewer stereotypical movements and smiling but had a few incidents of "staring". EEG revealed incorrect spelling with localized paroxysmal lesions during somnolence. A year later she still did not develop speech, presented atactic gait, stereotypes escalated and drooling with bruxism occurred. At the age of 12 she was diagnosed with systemic scleroderma and was treated with methotrexate. At the age of 13 epilepsy was diagnosed and two epileptic episodes have appeared so far.

The girl does not speak until this day. She still presents stereotypical movements and profound intellectual disability, has also deep sensation disorders and elevated pain threshold.

Test	Age (yrs)	Result
Karyotype	2	46,XX
MS-PCR SNRPN	3,5	normal
FMR1 ((CGG)n)	4	normal
Array CGH	4,5	arr(1-22,X)x2
MECP2 (ex. 1,2,3)	5	normal







TUBGCP6 c.4358G>A (not reported in ClinVar)

TUBGCP6 c.5435_5436insG (VUS)

Genetic tests were performed in our patient. The results of karyotype and array-CGH were normal. The most frequent causes of Angelman and fragile X syndrome were excluded. Mutations in *MECP2* gene were not found. Whole-exome-sequencing revealed some variants of uncertain significance — one heterozygotic variant in *SCN1A* gene which can be responsible for epilepsy and familial hemiplegic migraine and two heterozygotic variants in *TUBGCP6* responsible for autosomal recessive microcephaly and chorioretinopathy. All of these variants are present in healthy father of our patient. The man admits having one epileptic episode in his childhood but negates taking any antiepileptic drugs.

Our patient underwent multiple genetic tests but still the cause of her symptoms remains unknown. Due to the presence of insignificant variants detected in WES both in patient and her father, those alterations cannot be recognized as genetic cause of the girl's phenotype.

21h30 - UNKNOWN CASE OF NEONATE POST IVF CONCEPTION WITH PHOCOMELIA, RIGHT SIDED DIAPHRAGMATIC HERNIA AND NO UNIFYING DIAGNOSIS FOLLOWING EXTENSIVE GENETIC INVESTIGATION

Presenting author: Karl Kavanagh

Dr. Karl Kavanagh¹; Dr. Shauna Quinn¹; Prof Sally-Ann Lynch¹; Prof Andrew Green¹

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Herein we present the case of a 2 month old girl with right sided congenital diaphragmatic hernia and phocomelia that has eluded diagnosis despite extensive genetic investigation.

She was born at 34 weeks' gestation. She was a dichorionic twin that was an assisted conception via IVF to non-consanguineous Irish parents, mother was 30 years old gravida 1, para 2. Antenatal ultrasound scan identified a large right diaphragmatic hernia containing much of the right lobe of the liver and marked right upper limb hypoplasia with just 2 rudimentary digits as well as intrauterine growth restriction; this was later confirmed on antenatal MRI. An amniocentesis was not undertaken due to an anterior lying placenta.

Birth was via elective caesarean section with immediate intubation following delivery. The second twin was and has remained well. Birth weight was 1.4kg (3rd centile), OFC was 29.5cm (22rd centile). Echocardiogram shortly after birth identified an ASD with left to right







shunt, large ductus arteriosus with bidirectional shunt, and a large PDA. Renal ultrasound was normal. Cranial ultrasound identified a left grade 1 subependymal haemorrhage.

She had an early post-natal ArrayCGH and Trio Whole Exome Sequence were both non-diagnostic. Due to the history of diaphragmatic hernia buccal FISH was done for Pallister-Killian and karyotope which were also negative. A skin biopsy was taken for karyotype which was likewise non-diagnostic.

The patient remains on ventilator support in ICU. No unifying diagnosis with respect to genetic aetiology has been made. Advice on possible diagnoses or investigations would be greatly appreciated.



Phocomelia (ectrodactyly) of right upper limb

21h40 - SPLENOMEGALY — PATHOGNOMIC OR ADDITIONAL FINDING?

Presenting author: Karolina ŚLEDZIŃSKA

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Introduction: Splenomegaly may be caused by several factors: liver disease, venous thrombosis, hematologic malignancies, splenic congestion, infection, connective tissue diseases, focal lesions. Some disorders may be hereditary or genetic: splenic sequestration (pediatric sickle cell disease, hemolytic anemias, thalassemias), infiltrative disorders (glycogen storage diseases).

Patient: We would like to present a case of 4 years old boy with a history of splenomegaly. Born as 2nd pregnancy, 2nd labour, naturally, 39 hbd, Apgar 9; perinatally transient adaptive respiratory disturbances. Prenatal history unsignificant. From the first year of life child suffered from mild recurrent viral infections (chickenpox, bronchiolitis, gastroenteritis, pneumonia, cold). Lab blood tests revealed mild microcytic anaemia (Hb10.4 g/dl, MCV 70.7, MCH 22.8, blood smear normal), decreased ferritin level. Microbiology differential diagnosis test were performed – all negative (Toxocarosis, HCV, HBV, HIV, EBV, parvovirus B19, TOXO, CMV). Allergology specific IgE panel – negative. Spherocytosis EMA test – negative. Immunoglobulins (IgA, IgG, IgM) levels - normal. T/B lymphocytes – results pending.Urine – increased UPCR, B-microglobulin – awaiting nephrology consultation. Metabolic screening: urine mucopolisacharides - negative, CDG – negative, MPS/ Gaucher/ Nieman Pick – enzymatic negative, lactate, ammonia, ABG – normal. On abdominal USS/MRI – enlarged spleen with homogenous consistency, slightly enlarged liver and signs of tubulopathy. On USS – transiently enlarged normal cervical lymphnodes. Head MRI – normal.

Consultations: ENT – enlarged pharyngeal and palatine tonsils – adenotomy and tonsillectomy was performed, Audiology Clinic – mild deafness, Cardiology – normal ECHO, Ophtalmology – difficult to perform due to lack of cooperation with patient the retina visible from below, normal, pink, adherent, vessels with normal dimensions, the macula could not be examined, Neurology – speech and psychomotor development delay. On examination (photography will be attached to presentation) dysmorphic facial features, microcephaly, chest deformity, splenomegaly, distended abdomen.

Results: Karyotype, aCGH – normal. WES: patient is heterozygous for TFAP2B c.182C>T, p.(Pro61Leu) (VUS) related to Char syndrome, heterozygous for SMARCA2 c.1226C>T, p.(Ala409Val) (VUS) related to Nicolaides-Baraitser syndrome, hemizygous for NDUFB11 c.44C>A, p.(Ala15Glu) (VUS), related to linear skin defects with multiple anomalies. Parental analysis is pending.

Conclusions: None of the above mentioned syndromes has splenomegaly in its clinical picture. In our opinion there is the most resemblance with the Nicolaides Baraitser syndrome, but we would like to discuss the case with an audience for further potential diagnostic differential.

21h50 - AN UNKNOWN CASE OF CONGENITAL KIDNEY DEFECT, SEVERE MICROCEPHALY, AND INTELLECTUAL DISABILITY

Presenting author: Klaudia Berk

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Here, We describe an unknown case of 7 years old boy. He was born on time, naturally, from the 3rd pregnancy and the 1st delivery to healthy, unrelated parents (his mother had miscarried two previous pregnancies). Prenatal history was negative for exposure to drugs and teratogens. Fetal USG showed an enlarged, polycystic right kidney. Birth parameters were: weight- 3620g (71 pc), length - 58 cm (100pc), OFC - 33cm (12 pc), Apgar score 10/10. The neonatal period was complicated by hyperbilirubinemia (phototherapy). Immediately after birth kidney dysplasia was confirmed on USG. Moreover, transfontanelle USG revealed cephalhematoma and the slight asymmetry of the lateral ventricles.



A 7-month-old patient was referred to genetic counseling due to a congenital renal defect and dysmorphic features. On physical examination, he presented craniofacial dysmorphism including significant microcephaly (OFC: 35 cm, 0.0 pc) and the spasticity of the upper limb. MRI CSN was normal. Nowadays, 7 years old boy is 122 cm (39 pc) tall, he weighs 20 kg (10 pc) and his OFC is 46 cm (0.0 pc). He has a mild intellectual disability. Psychomotor development is delayed. He uses single words, he doesn't make logical sentences. He has learning difficulties and problems with interpersonal contacts. EEG is abnormal with no visible seizures.

Performed karyotype was 46, XY. MLPA and aCGH were also normal. NGS of 820 genes associated with microcephaly found no pathogenic mutations.

Suggestions of a clinical or genetic diagnosis are welcome.

22h00 - AN UNSOLVED CASE OF SYNDROMIC OBESITY WITH INTELLECTUAL DISABILITY, SPASTIC PARAPARESIS, AND DYSMORPHISMS

Presenting author: Mafalda Melo

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Case presentation: We describe an 8-years-old girl referred for obesity associated with intellectual disability, spastic paraparesis, and dysmorphisms. She is the only child of healthy, non-consanguineous parents. From family history, we stand out the father with polydactyly and two first paternal cousins with global developmental delay. Prenatal and perinatal periods were uneventful.

Dysmorphologic examination: She is obese (>P97, +3.5sd) and shows a wide based ataxic gait. She presents a syndromic gestalt with highly arched full eyebrows, synophrys, depressed nasal bridge, upturned nose, slightly open mouth with tented upper lip, and lobulated tongue. She also has acanthosis nigricans, genu valgus, brachydactyly, and 2nd and 3rd toes syndacthyly (Figure 1).

Investigations: Previous CNS imaging and metabolic screening were normal. Genetic testing, including microarray and whole exome sequencing (single-analysis) were also normal. We thank you for your collaboration in achieving a possible clinical diagnosis or any suggestion to additional investigation. The identification of a molecular etiology would impact the prognosis, management, and accurate genetic counselling for the family.



Figure 1. Our patient at 8-years-old.

22h10 - UNKNOWN DIAGNOSIS - DEVELOPMENTAL DELAY AND DYSMORPHIC FEATURES

Presenting author: Maria Abreu

Maria Abreu1, Cláudia Falcão Reis1

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We present the clinical case of a child, female, 8yo, first seen in medical genetics consultation at 2 years of age due to developmental delay and microcephaly.

The child was born at term, with 40 weeks of gestational age, with normal weight and length, but head circumference below the 5th centile, and postural plagiocephaly.

She was hypotonic since the neonatal period. She also presented a patent arterial duct, high myopia, supernumerary nipples and an occult spina bifida. Through follow-up, she was diagnosed with developmental delay and later intellectual development disorder, with a global IQ of 49 at 7yo through WISC-III evaluation. Dysmorphologic examination found brachycephaly and mild plagiocephaly, highly arched eyebrows, hypertelorism, bilateral epicanthus, midface hypoplasia, small widely spaced teeth, pointy chin, and prominent ears with an anteverted lobule. Genetic testing included microarray and clinical exome. These disclosed a subtelomeric microduplication in chromosome 18q and heterozygous VOUS in genes *NIPBL* and *KMT2D*, all inherited from a healthy parent. Other variants were reported but were not compatible with the patient's phenotype.

Input from an expert panel would be welcome in the diagnostic workup.

22h20 - A PATIENT WITH A POLYMALFORMATIVE SYNDROME WHOSE MOLECULAR CAUSE REMAINS UNKNOWN

Presenting author: Susana Lemos Ferreira

Authors (Susana LEMOS FERREIRA¹, Margarida VENÂNCIO¹, Marta AMORIM¹)

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Case report: A 6-years-old female was first referred to our outpatient genetic department at neonatal period with a polymalformative syndrome. She was the first child of non-consanguineous parents with a family history of severe psychiatric disease and craniosynostosis. Pregnancy was complicated with gestational diabetes. Invasive prenatal diagnosis was performed through amniocentesis due to advanced maternal age, and a karyotype was completed with a normal result (46,XX). At the third trimester ultrasound a single umbilical cord and a mild ventriculomegaly were identified.

The patient was born at 37 weeks and 5 days of gestation with low birth weight, respiratory distress that required mechanical ventilation and was transferred to the neonatal intensive care unit. At our observation she showed trigonocephaly, facial asymmetry, small hypopigmentation patch in the right temporal region, mid face hypoplasia, anteverted nares, brachydactyly, and anterior anus. A maxilla-mandibular CT was performed that identified an incomplete choanal atresia. MRI confirmed ventriculomegaly. Echocardiogram revealed a







patent foramen ovale, mild mitral regurgitation, and patent arterial duct that required a transcatheter closure. Abdominal imaging identified mild hepatomegaly.

At 2-years-old she was diagnosed with bilateral peripheric subtotal cataracts, partial iris heterochromia and recurrent blepharitis. Additional medical findings included metopic craniosynostosis, congenital torticollis, Achilles tendon shortening, and global developmental delay. A subsequent MRI identified a supratentorial ventriculomegaly, unilateral agenesis of parotid gland, and spinal cord anchored in a fibrous tractus that is embedded in a subcutaneous lipoma.

Extensive investigation was performed with normal chromosomal microarray analysis and exome. Considering a possible *FGFR2* related disorder, a molecular study of *FGFR2* gene was also completed, but no further pathogenic variants were identified.

This case remains without a molecular diagnosis that could offer an appropriated genetic counselling and a better surveillance to this patient and family. By presenting this case, we hope that it's discussion can bring us one step closer to a possible molecular diagnosis.



Fig.1 Our patient with 1-year-old and 2-year-old (left to right)

22h30 - DIAGNOSTIC ODYSSEY QUEST FOR A DYSMORPHIC GIRL WITH INTELLECTUAL DISABILITY

Presenting author: Joana Catanho

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We report a 15 year-old girl, second child of non-consanguineous parents. At 27 weeks of gestation, mother underwent amniocentesis due to fetal microcephaly. Conventional cytogenetics identified an abnormal fetal karyotype: 47,XX,+r[2]/46,XX[79]. Fluorescence in situ hybridization (FISH) did not identify the marker-chromosome. She was born at 38 weeks of gestation with a weight of 2770g (9th percentile), a length of 47 cm (9th percentile) and a OFC of 31.5 cm (< 1st percentile, -2SD). At observation, she presented facial asymmetry, broad nasal bridge, large ear lobes, thin lips, microretrognathia, long halluces and hypertrichosis. Recent examination at our clinic describes a girl with microcephaly (-3SD), severe intellectual disability, hand stereotypies and mood swings. The patient has no language and presents limited movements and spasticity of the lower limbs. Other dysmorphic features now observed include: thick eyebrows, long eyelashes, long palpebral fissure, convergent strabismus, kyphoscoliosis She was also diagnosed with sensorineural hearing loss, celiac disease, recurrent infections, and sleep apnea.

Chromosomal microarray (CMA) analysis was normal. Clinical exome identified a heterozygous variant of unknown significance in *KMT2S* [(NM_003482.3) - c.8314C>T (p.(Leu2772Phe)] gene which is associated with autosomal dominant Kabuki Syndrome. This variant was inherited from a healthy mother.

Whole-genome sequencing is ongoing.











DAY 3 – FRIDAY 16th OF SEPTEMBER

09h00 - SESSION 7, FETAL PATHOLOGY (Chair: Koen Devriendt)

9h00 – A NOVEL STRA6 VARIANT IN TWO FETUSES WITH MALFORMATIONS OF PDAC SYNDROME

Presenting author: Madeleine Joubert

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PDAC (Pulmonary hypoplasia/agenesis, Diaphragmatic hernia/eventration, Anophthalmia/microphthalmia, Cardiac defect) syndrome is a severe congenital multisystem disorder characterized by constant ocular defects such as anophthalmia/microphthalmia associated with a broad spectrum of malformations involving pulmonary, diaphragmatic, heart, renal and/or genital defects. This condition is associated with biallelic pathogenic variants in *STRA6*, which plays a crucial role in cellular uptake of vitamin A. To date, less than 30 families with a molecular diagnosis have been reported, displaying high inter- and intrafamilial clinical variability. Most of affected individuals have been assessed after birth, with only few antenatal data available in the literature.

We describe two fetuses from a consanguineous couple presenting clinical manifestations of PDAC syndrome. Targeted sequencing of *STRA6* identified a new homozygous pathogenic variant (NM_022369: c.1167-2_1169delinsTG) in the second fetus. This variant was predicted to affect splicing by *in silico* predictions tools. mRNA analyses confirmed the use of a cryptic acceptor site leading to a frameshift insertion. During pregnancy, orbital defects are difficult to detect and prognosis is based on additional features that are inconstant. This highlights the importance of post-mortem examination to guide the etiological diagnosis. We aim to further describe the perinatal presentation of this condition.

Figure I. Pedigree, clinical features and *STRA6* variantal status of family.

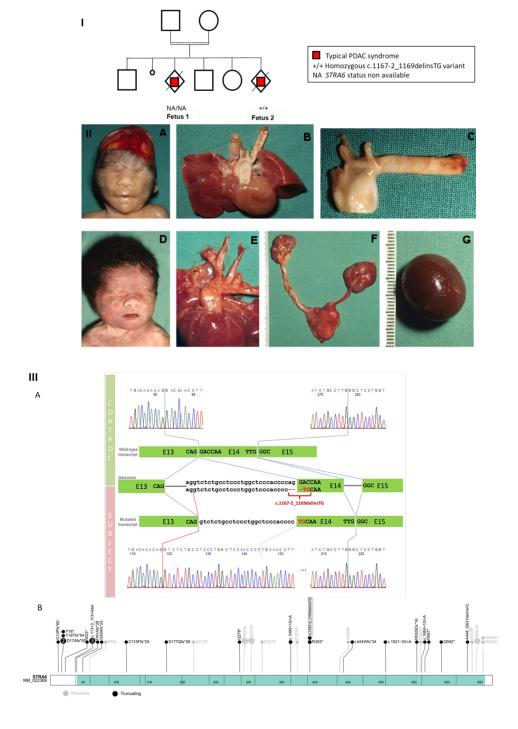






Figure II. *Fetus II-3*: narrow depressions at the site of palpebral fissure, hirsutism, proeminent nose (A), lungs hypoplastic and unilobar, complex heart malformation with hypoplastic left heart (B), and hypoplastic ascendant and horizontal aorta (C). *Fetus II-3*: apparent anophthalmia, hirsutism, proeminent nose with anteverted nares (D), cardiac anomaly on the type of truncus arteriosus (E), hypoplastic right kidney with dilated ureter and pelvic left kidney (F), unusual morphology of the spleen (G).

Figure III. mRNA study on muscle tissue. Homozygous Indel is confirmed in the subject. A cryptic splice site is used leading to the retention of the last 26 nucleotides on the intron 13.









9h15 – SEVERE FETAL PHENOTYPE ASSOCIATED WITH A DE NOVO MUTATION IN TUBA1A, ALREADY DESCRIBED BEFORE IN A MILDLY AFFECTED BOY

Presenting author: Julie Désir

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We describe an antenatal case of tubulinopathy. The clue for the diagnosis was the association of infra and supratentorial cerebral anomalies at fetal imaging. This suspicion was confirmed by clinical exome that demonstrated a de novo mutation in *TUBA1A*.

Tubulinopathies due to de novo mutations in *TUBA1A* are frequently associated with major cortical malformations including lissencephaly (agyria-pachygyria), polymicrogyria or polymicrogyria-like cortical dysplasia and cortical gyral simplification. Subcortical anomalies affecting the corpus callosum, the cerebellar vermis, the brainstem, the basal ganglia and the cerebellum are also described.

Prenatally diagnosed fetal cases show a more severe phenotype than born individuals in the literature. Interestingly, the variant c.368G>A, p.(Arg123His) found in the fetus by clinical exome was responsible of a severe fetal phenotype, and was already described before. This variant that was classified as pathogenic has been identified in a mildly delayed 18 monthsold boy, previously reported by Romaniello et al. (Eur Radiol, 2017 PMID:28677066).

We compare the prenatal phenotype of the fetus and the postnatal phenotype of the reported case.

9h30 - FETAL DIAGNOSIS OF A NEW TUBB3 VARIANT LINKED WITH DISTORTION OF THE INTERHEMISPHERIC FISSURE AND HIGH INTRAFAMILIAL PHENOTYPIC VARIABILITY

Presenting author: Abdelhakim Bouazzaoui

<u>Abdelhakim Bouazzaoui</u>¹, Paul Rollier¹, Erika Launay³, Céline Rozel⁵, Marie Faoucher^{2,4}, Auriane Cospain¹, Wilfrid Carré^{2,4}, Chloé Quélin¹, Sylvie Odent¹

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We report on a new pathogenic variant in *TUBB3* gene including three individuals from the same family, including an adult, a female child and a male fetus. All carrying a novel pathogenic heterozygous missense variant c.259 C>T p.(Pro87Ser) in *TUBB3* gene.

Classically, *TUBB3* pathogenic variants are associated with basal ganglia dysmorphism, frontal polymicrogyria, simplified and disorganized gyral patterning, thin corpus callosum, and brainstem and cerebellar vermian hypoplasia.

Here, all affected individuals display an anterior Distortion of the InterHemispheric Fissure (DIHF) with abnormal left ventricle morphology; other brain malformations are associated including atrophy of the left thalamus and lenticular nucleus, lack of left sylvian fissure operculization, asymmetry of gyration of olivary bodies, pyramids and inferior part of the pons. We can observe intra-familial phenotypic variability: The child evolved with moderate psychomotor delay, hypotonia, spasticity, poor fine and gross motor skills and a heterogeneous cognitive profile, the mother had difficulties in coordination and walking delay but achieved standard education and normal socio-professional integration.

Prenatal DIHF case was previously reported only once in link with a *de novo TUBB3* variant, our observation adds three additional cases including a prenatal one. DIHF seems to be a finding that can strongly suggest tubulinopathy-spectrum associated brain malformations.

9h45 - NON-IMMUNE FETAL HYDROPS AND PRENATAL-ONSET CHYLOTHORAXAN UNUSUAL PRESENTATION FOR CM-AVM SYNDROME DUE TO THE HETEROZYGOUS VARIANT c.2923delG p.Asn976fsTer19 IN THE *RASA1* GENE

Presenting author: Livia Garavelli

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Variants in the *RASA1* gene are typically associated with a clinical condition called "Capillary Malformation-Arteriovenous malformations" (CM-AVMs), an autosomal dominant genetic disease with variable phenotype and finding of multifocal capillary malformations and arteriovenous malformations (fast-flow lesions) localized preferentially in the central nervous system, but also at the cutaneous, spinal and multiorgan level. Despite the presence of numerous reports in the literature regarding variants of *RASA1* and diagnosis made in childhood / adulthood, only 6 reports are reported with onset of clinical features in the







prenatal period (Overcash R., 2015, Macmurdo C., 2016, Nicholson P., 2019, D'Amours G., 2020, Gallipoli A., 2021) with non-immune fetal hydrops and/or chylothorax.

We present the case of a newborn with non-immune fetal hydrops and prenatal onset chylothorax with heterozygous variant c.2923delG p.Asn976fsTer19 in the RASA1 gene.

Prenatal history: the obstetric ultrasound at the 28th week showed bilateral pleural effusion and severe pericardial effusion with polyhydramnios that made positioning of thoracic-amniotic shunt necessary. Microscopic analysis of the pleural fluid at birth: diagnosis of chylothorax on sampling performed at 6 days of life and diagnosis of non-immune hydrops fetalis with pleural effusion and hydropericardium. The newborn had no cutaneous vascular anomalies at birth, but we evaluated the newborn's skin again at the age of 2 months and 20 days: the small capillary malformations of round or oval shape were evident. The intracranial arterial MRI angiography study showed normal caliber of the carotid siphons, of the vessels of the polygon of Willis, of its main branches and of the vertebrobasilar axis. At the age of 3 months a thoracoscopy-thoracotomy was necessary, with cleaning of the pleural cavity and detection of a red-purple 2-3 cm angiomatous growth at the level of the posterior-superior wall of the pleuric cavity.

We evaluated the mother's skin and the brother's skin: they both have multiple, small capillary malformations of round or oval shape. The clinical features are fully compatible with the diagnosis of a RASA1-related condition.

The NGS analysis with the study of the RASopathies genes and the *RASA1* gene revealed the heterozygous variant c.2923delG in the RASA1 gene, which at the protein level determines the introduction of a premature stop codon p. Asn976fsTer19. The frameshift variant, with maternal segregation, is not present in the database of allele frequencies of the general population (gnomAD), was not described in scientific literature and can be classified according to the ACMG guidelines as a pathogenetic variant. The segregation analysis showed the same variant in the brother.

CONCLUSIONS: 1) In case of congenital chylothorax and non-immune hydrops fetalis: consider *RASA1*-related conditions in the differential diagnosis. 2) Examine the skin of the 1st degree relatives, who may not know they are affected 3) Skin vascular abnormalities may not be evident in the newborn, but may appear after a few months 4) It is important to make a correct diagnosis because there may be arteriovenous brain malformations.

References

Swearingen C et al. Nonimmune Hydrops Fetalis, Clin Perinatol, 2020 Gallipoli A et al. Congenital Chylothorax and Hydrops Fetalis: A Novel neonatal presentation of RASA1 Mutation, Pediatrics, 2021

Durrington HJ et al. et al. A novel RASA1 mutation causing capillary malformationarteriovenous malformation (CM-AVM) presenting during pregnancy. Am J Med Genet A. 2013

Nicholson P et al. The protean manifestations of RASA1 gene mutation, Clinical and Experimental Dermatology, 2019

Overcash RT et al. Maternal and fetal capillary malformation—arteriovenous malformation (CM–AVM) due to a novel RASA1 mutation presenting with prenatal non-immune hydrops fetalis. Am J Med Genet Part A, 2015

Revencu N et al. RASA1 mutations and associated phenotypes in 68 families with capillary







malformation-arteriovenous malformation. Human Mutation, 2013
Macmurdo CF et al RASA1 somatic mutation and variable expressivity in capillary
malformation/arteriovenous malformation (CM/AVM) syndrome. Am J Med Genet, 2016
D'Amours G et al Prenatal pleural effusions and chylothorax: An unusual presentation for
CM-AVM syndrome due to RASA1. Am J Med Genet, 2020

10h00 - WHAT IF WE HAD KNOWN OF THOSE RIBS BEFORE?

Presenting author: Bernardo Rinaldi

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We describe the case of a family with two consecutive fetuses presenting with multiple congenital anomalies. The two fetuses underwent prenatal ultrasound, autopsy, radiologic and genetic investigation. Genetic analysis included karyotype and array-CGH for both fetuses and trio-based whole exome sequencing (WES) only for the second fetus. WES results, focusing on recessive or dominant *de novo* variants, were first negative. However, as a result of new relevant information regarding family history, we were able to reach the molecular diagnosis, shared with the mother.

With this case we would like to stress:

- how WES data analysis and interpretation strongly rely on family history and robust genotype-phenotype correlation; this is even more relevant in the prenatal setting, where access to fetal phenotype is limited and prenatal recognition of many morbid genes is not fully explored
- a detailed description of the prenatal manifestations of the underlying syndrome, which is not usually considered among those providing fetal malformations
- one key element of the reverse phenotyping (ribs) was disclosed by means of autoptic TC scans; notably, ultrasounds findings were not suggestive for a skeletal condition, making the diagnosis serendipitous and leading us to reflect about investigations requested after the termination of pregnancy
- as recently described also by other groups, from this case we have learned how filtering out inherited variants from apparently healthy parents may be misleading







10h15 - CLINICAL CHARACTERIZATION OF 6 ADDITIONAL CASES WITH A ARCN1 MUTATION: FROM SEVERE FETAL PRESENTATION TO A RECOGNIZABLE CRANIOFACIAL SHORT STATURE SYNDROME

Presenting author: Marjan DE RADEMAEKER

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Introduction: The archain 1 (ARCN1) gene encodes the coatmer subunit delta of coat protein complex I (COPI) involved in intracellular protein transport.

Loss-of-functions variants in *ARCN1* have been associated with *ARCN1*- related syndrome with a clinical spectrum from a severe fetal presentation with skeletal anomalies to a less severe form with intrauterine growth retardation, short stature with rhizomelic shortening, facial features as microretrognathia and risk of developmental disorder. Recently also systemic features like transient liver dysfunction has been described. To date a total of 20 patients has been described in the literature.

Methods: We report six additional patients (two fetuses and four patients) from four different families with loss-of-function *ARCN1* variants. We describe genetic and clinical data (facial and skeletal phenotype, growth and development), compare our data with those previously reported and further delineate the phenotypic characteristics.

Results: All *ARCN1* variants are loss-of-function variants with one variant (p.Arg170*) already reported in the literature.

The clinical characteristics (as IUGR, short stature and microretrognathia) seen in our four patients are comparable to the previously reported with transient liver dysfunction in two of our patients. We report furthermore two fetuses with a severe prenatal presentation including skeletal features and brain anomalies. One of the fetuses was part of a family in which the mother and maternal grandfather have a milder phenotype although with typical clinical characteristics.

Conclusion : These novel cases of *ARCN1*- related syndrome confirm the wide clinical spectrum of the disease and although characteristics are similar, they broaden the phenotypic spectrum and show the intrafamilial variability in disease severity







11h00 - SESSION 8: SYNDROME DELINEATION (Chair: Alma Küchler)

11h00 – INVITED TALK, JULIETTE NECTOUX: NON-INVASIVE PRENATAL DIAGNOSIS OF SINGLE GENE DISORDERS. WHERE ARE WE NOW AND WHERE ARE WE GOING?

11h45 - MANIFESTATIONS OF A HETEROZYGOUS CDK13 MUTATION AS A RARE ENTITY; CONGENITAL HEART DEFECTS, DYSMORPHIC FACIAL FEATURES, AND INTELLECTUAL DEVELOPMENTAL DISORDER

Presenting author: Alp Peker

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Congenital heart defects, dysmorphic facial features, and intellectual developmental disorder (CHDFIDD) is a disease occurring with a heterozygous mutation in CDK13 gene located in 7p14.1 (OMIM: 603309) with less than fifty published cases in the literature. Patients of this disorder almost all display a lack of verbal skills at ages older than one, behavioral abnormalities and traits of autism such as stereotypies, distinct facial features, structural changes to heart, and difficulty of feeding in infancy.

Our case, now 7 years old, first presented to us with a history of umbilical hernia, dilated cardiomyopathy, and mitral regurgitation of second degree. Patient was born at 38 weeks, 2750 grams to a mother with gestational diabetes with no parental consanguinity. During routine physical examination a heart murmur of grade 3 was present, an echocardiography was performed indicating a diagnosis of dilated cardiomyopathy within first month of life. Later, he was consulted to our pediatric genetics clinic due to additional features of facial dysmorphism especially noticed as micrognathia. In our clinic, the patient was observed to have dysmorphic findings of low set dysplastic ears, flat face, periorbital fullness, epicanthus inversus, broad nasal root, thin upper lip, high arched palate, retromicrognathia with widespread mongolian spots.

Chromosome analysis was performed revealing a normal karyotype. His eye examination and hearing test had shown no pathologies. His metabolic tests resulted to be normal. 15 months old, our patient was followed with neuromotor developmental delay, psychometric analysis' confirmed delay in all stages. At the age of 3, he was unable to form meaningful







words and showed signs of autism spectrum disorder. After micro-array analysis resulted with no copy number variation, the patient was lead to whole exome sequencing (WES).

The WES analysis revealed a heterozygous variant of c.2525A>G in a highly conserved area in exon 6 of CDK13 (NM_003718.5) gene, classified as pathogenic, meeting the criteria of ACMG, in disease specific databases such as VarSome, ClinVar. Gene itself encodes a member of serine/threonine protein kinase which phosphorylates cyclin K. The amino acid alteration caused by the variant c.2525A>G (p.Asn842Ser) was expected to exhibit a total loss in protein function, hence the loss of ATP binding to the kinase, therefore it's predicted to have a pathogenic effect by in-silico analysis'. Parents of the patient, afterwards, were forwarded to WES analysis and a normal result was seen, confirming the variant of our patient as a de novo mutation.

As there are several published cases, statistical power to evaluate genotype-phenotype correlation is diminished, yet the variant and clinical presentation of our patient were consistent with the literature. Eventually proving that publishing of more cases is necessary for better understanding CDK13 and its mutations' effects on phenotype.

12h00 - COMPLEX CRANIOSINOSTOSIS AND CONGENITAL GLAUCOMA IN CDK13-RELATED DISORDER: A CASE REPORT

Presenting author: Contrò Gianluca

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The cyclin-dependent kinases (CDK) family is a group of proteins involved in different cellular processes such transcription, regulation of the cell cycle and splicing. Variants in these genes have been linked to different clinical conditions, mostly characterized by intellectual disability, malformations in the central nervous system, microcephaly and cancer. Among the 21 human CDK genes, variants in *CDK13* have recently been linked to a novel syndromic clinical condition characterized by congenital heart defects, intellectual disability and peculiar facial dysmorphisms (Congenital Heart Defects, Dysmorphic Facial Features, and Intellectual Developmental Disorder; CHDFIDD. OMIM # 617360).

To date, 62 patients have been reported, all with a similar clinical picture and with a *de novo* missense or splicing variant in *CDK13*. All pathogenic variants are located in the protein-kinase domain of the protein, suggesting that this region is essential for the normal function of the genetic product. Because the group of patients reported to date is small, the specific phenotypic spectrum is still under definition. Intellectual disability, usually mild to moderate, is almost universally present. Structural brain abnormalities (such as hypoplastic corpus







callosum, Chiari malformation, syringomyelia) and cardiac malformations (comprising atrial or ventricular septal defect) have been reported and they are part of the main clinical findings in this condition.

Here we described a patient with a *de novo* missense variant in *CDK13* that showed a cardiac defect, intellectual disability, some typical dysmorphisms and neuroradiological anomalies and a wide range of skeletal features, but she also exhibited some unique features not previously reported. The main characteristic consisted of a complex Pfeiffer-like craniosynostosis, due to a premature closed metopic suture and a right partially-fused lambdoid suture. Because of the complexity of the malformation, the patient underwent surgical correction at 2 years of life. To date, only three patients reported have shown craniosynostosis and one has required surgical correction; none of these individuals exhibited a complex cranial morphology similar to our patient. It could also be hypothesized that some anomalies of the facial phenotype (such as hypo / hypertelorism or a wide nasal bridge) could be the consequence of an underlying unrecognized cranial anomaly.

Furthermore, our patient exhibited congenital bilateral glaucoma, never reported before. Regarding her skeletal feature, scoliosis with kyphosis, asymmetric shoulders and *pectus carinatum* have been observed as well. Finally, unlike the other patients, a diffuse reduced joint mobility has been noted at the elbow and at the hands with stiff metacarpophalangeal joints.

Our report has led to broadening and strengthening knowledge of the clinical spectrum of CHDFIDD, highlighting some less common clinical signs that are useful as a diagnostic tool for suspecting and diagnosing this condition.

12h15 - BLAKEMORE-DURMAZ-VASILEIOU (BDV) SYNDROME: A NOVEL SYNDROME WITH PROFOUND OBESITY AND NEURODEVELOPMENTAL DELAY RESEMBLING PRADER-WILLI SYNDROME

Presenting author: Georgia Vasileiou

<u>Georgia VASILEIOU¹</u>, Elisabeth BOSCH¹, Moritz HEBEBRAND¹; Bernt POPP², Theresa PENGER³, Bettina BEHRING³, Helen COX⁴, Shelley TOWNER⁵, Cornelia KRAUS¹, William G. WILSON⁵, Shagufta KHAN⁴, Mandy KRUMBIEGEL¹, Arif B. EKICI¹, Steffen UEBE¹, Regina TROLLMANN³, Joachim WOELFLE³, André REIS¹

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Early childhood obesity in combination with neurodevelopmental delay is a relatively frequent presentation in genetic clinics. Aetiological diagnosis though is challenging, as the so far described 55 syndromes are responsible for only a small subset of cases. CPE encodes carboxypeptidase E enzyme, which directs proneuropeptides and prohormones to the regulated secretory pathway and converts them to bioactive forms. Previously, four individuals from two consanguineous families with morbid obesity, neurodevelopmental delay and endocrine anomalies harbouring biallelic loss-of-function CPE variants were reported. Cpe-deficient mouse models exhibit slowly progressing obesity, degeneration of hippocampal neurons, memory deficits, behavioural anomalies and diabetes. Here we report four individuals from three unrelated consanguineous families, two siblings of Syrian, one of Egyptian and one of Pakistani descent, all carrying novel causative biallelic loss-of-function variants in CPE. Prader-Willi syndrome (PWS) was initially suspected and excluded for all herein described cases. Exome sequencing revealed the biallelic variant p.(Arg121*) in Syrian siblings. The same change was identified in the Egyptian individual, whereas the Pakistani individual harboured the variant p.(Ser333Alafs*22). By comparing affected individuals' phenotypes to those of the four previously reported cases, a novel syndrome with a recognisable clinical presentation could be delineated, which we named Blakemore-Durmaz-Vasileiou (BDV) syndrome. Major clinical features of BDV syndrome include neurodevelopmental disorder with moderate intellectual disability, severe speech delay and mild to moderate motor delay, mild infantile hypotonia, morbid obesity with onset of weight gain between 6 months and 4 years, hyperphagia, hypogonadotropic hypogonadism and hypothyroidism. Rarer clinical findings included behavioural disorders, insulin resistance and diabetes mellitus type 2. With the exception of failure to thrive in infancy and severe neonatal hypotonia, BDV syndrome has common clinical manifestations with PWS in early and late childhood. Based on the probability of LoF intolerance score (pLI = 0.99) the CPE gene seems to be highly intolerant to heterozygous truncating variants, suggesting that a heterozygous state may also be associated with a milder phenotype. Computational analysis indicated that the functional and C-terminal domains of CPE are highly conserved and intolerant not only to loss-of-function variants but also to missense variants. Our findings suggest that missense variants may also be clinically relevant, thus requiring careful examination before classification as benign variants. In summary, we establish BDV syndrome as a novel autosomal recessive genetic entity clinically overlapping with PWS syndrome.

12h30 - MOLECULAR CHARACTERIZATION OF AN EMBRYONAL RHADOMYOSARCOMA OCCURING IN A PATIENT WITH KABUKI SYNDROME: REPORT AND LITERATURE REVIEW IN THE LIGHT OF TUMOR PREDISPOSITION SYNDROMES

Presenting author: Sietse Aukema

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Introduction: Kabuki syndrome (KS) is a multiple congenital abnormality/intellectual disability syndrome in which the majority of the patients has a *KMT2D* germline variant. With the publication of several case reports of patients with KS and a concomitant malignancy the topic of tumor predisposition in KS has received increased attention. Moreover, somatic *KMT2D* variants can be found in 5-10% of tumors. We describe a patient with KS type 1 who developed an embryonal rhabdomyosarcoma (ERMS). To get more insight into a potential tumor predisposition in KS we performed molecular (epi)genetic analyses on tumor tissue and a literature review.

Methods: Exome sequencing and DNA-methylation profiling (EPIC-array) was performed on tumor DNA. For DNA methylation-based sarcoma classification we used the DKFZ-Sarcoma classifier (Koelsche, *Nat Commun* 2021). We conducted a literature search for reports of patients with KS and a concomitant malignancy.

Results: DNA-methylation profiling mapped the case to ERMS. Exome sequencing revealed variants in *ERCC5* and *TP53*. Copy number variant analysis revealed (partial) gains of chromosomes 2,3,7,8,12,15, and 20, and 3 focal deletions in 11p. Sanger re-sequencing of the germline variant suggested a gain of the wild-type *KMT2D* allele in the trisomy 12. No second (likely)pathogenic variant in *KMT2D* was identified. Including our patient literature review identified 18 patients with KS and a malignancy. Overall, the landscape of malignancies in patients with KS was reminiscent of that of the pediatric population in general. No secondary malignancy, bilateral-/multifocal or meta-synchronous malignancies were reported. Histopathological and molecular data were infrequently reported and did not include next generation sequencing and/or DNA-methylation profiling.

Conclusion: Although, based on our (molecular) analyses and literature review, a tumor predisposition cannot be confirmed or ruled out, we found no strong arguments pointing towards KS as a tumor predisposition syndrome.

Grants: Sietse M. Aukema is a "Ton van Essen Award" winner of the Dutch Clinical Genetics Society (VKGN).

12h45 - EXPANDING THE PHENOTYPE OF DPH1-RELATED LOUCKS-INNES SYNDROME: TWO SIBLINGS WITH ECTOPIC NEUROHYPOPHYSIS CAUSED BY BI-ALLELIC VARIANTS IN DPH1

Presenting author: Jeroen Breckpot

Laurens Hannes^{1,2}, Marc Gewillig^{3,4}, Koen Devriendt^{1,2}, Jeroen Breckpot^{1,2}







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Germline bi-allelic loss-of-function variants in the gene for diphthamide biosynthesis protein 1 (DPH1) were linked in 2015 to an ultra-rare and severe cause of neurodevelopmental delay with short stature, dysmorphic facial features and ectodermal anomalies, such as sparse hair on the scalp and the eyebrows. Additional features include limb and central nervous anomalies. To date, 18 patients have been described in literature with predominantly homozygous mutations. Here we describe a 19-year-old female who was the first child of non-consanguineous parents. She was born with short stature, hypotonia, failure to thrive, perimembranous ventricular septum defect, bilateral postaxial polydactyly, oxycephaly, nasal hypoplasia, microphthalmia, cutaneous hemangioma and the absence of eyelashes. Imaging by MRI showed an ectopic neurohypophysis and atlantooccipital fusion. Her younger sister showed similar features, including ectopic neurohypophysis and a more severe cardiac phenotype, featuring ventricular septal defect, pulmonary stenosis and atrial septal defect secundum type. She died at 4 months due to postoperative complications. A younger brother is in good health. No (likely) pathogenic variants were found by conventional and molecular karyotyping, nor by clinical exome analysis in 2015. Subsequently, quad whole genome sequencing (WGS) analysis was performed including WGS analysis from the healthy brother. WGS showed compound heterozygosity for a predicted splice variant and missense variant in NM 001383 DPH1 (c.574-2A>G and c.G688C:p.A230P) in the index patient. These variants are absent in reference and patient databases, are in silico predicted to be damaging and are located in the diphthamide synthase domain. Parents and the healthy sibling were heterozygous carriers of one DPH1 variant. The phenotype of the affected siblings corresponds well to that of DPH1 syndrome, although the association of ectopic neurohypophysis and DPH1 is unprecedented, warranting neuroimaging and endocrine follow-up in all patients diagnosed with DPH1 syndrome.

14h00 – SESSION 9: SYNDROME
DELINEATION: unusual additional features
(Chair: Jeroen Breckpot)







14h00 - ARTHROGRYPOSIS IN PATIENTS WITH NEURODEVELOPMENTAL DISORDER DUE TO FOXP1 LOSS-OF FUNCTION VARIANTS

Presenting author: Christina Peduto

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Haploinsufficiency of FOXP1 gene has been recognized as the cause of a neurodevelopmental disorder presenting with intellectual disability (ID), autism spectrum disorder (ASD), speech delay, hypotonia, mild dysmorphic features, and congenital anomalies. We report four patients from unrelated families each harbouring novel heterozygous likely loss-of-function de novo FOXP1 variants, including two nonsense, one splice variant and a whole gene deletion. All four patients showed developmental delay with moderate to severe speech delay, ID, ASD and facial dysmorphic features, including broad forehead, down-slanting palpebral fissures, short nose with broad tip, ptosis, and hypertelorism. Moreover, multiple congenital contractures affecting two or more, both proximal and distal joints were observed.

FOXP1 has been implicated in neuronal differentiation and plays a critical role in defining the columnar identity of motor neurons at each axial position, as well as organising motor axon projections. Distal limb contractures have been reported in patients carrying de novo 3p14.1p13 microdeletion encompassing FOXP1 gene but not in cases with variants in FOXP1. We confirm that FOXP1-related disorder can be associated to joint contractures, supporting a key role of this gene in the development of limb specific motor neurons. Moreover, our cases illustrate that the combination of joint contractures and neurodevelopmental disorder should raise the clinical suspicion of FOXP1-related disease.

14h15 - DUAL DIAGNOSIS IN NEUROFIBROMATOSIS TYPE 1 WITH EPILEPSY OR INTELLECTUAL DEFICIENCY

Presenting author: Damien Lederer

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Neurofibromatosis type 1 (NF1) is one of the most frequent genetic disease. Main characteristics are café-au-lait (CaL) spots, neurofibromas, learning difficulties and behavior trouble. Due to its high frequency, it could be associated with other syndromes, recognisable or not. A recent study found association of neurofibromatosis type 1 with different recognisable syndromes such as Prader Willi, Down syndrome, Autosomal Dominant Polycystic Kidney Disease... (Muthusami et al. 2022).

Psychomotor delay and learning difficulties are frequent in children with neurofibromatosis type 1. Intellectual deficiency is present in 4-8% of children with NF1 and patients with an NF1 deletion are more likely to have intellectual disability (GeneReviews).

In our cohort of 22 patients with NF1, 13 patients had an additional neurologic phenotype such as learning difficulties, speech delay, epilepsy and 4 were too young (< 5 years of age) to evaluate their learning abilities.

Most of the patients were diagnosed through cDNA sequencing (Gent Genetic Centrum).

Four patients had diagnostic or complementary NGS analysis. One patient is carrier of an NF1-Noonan phenotype variant in NF1 (c.5489G>T; p.(Arg1830Leu)) without CaL spot diagnosed by exome. Another patient with febrile seizures, macrocephaly, developmental delay and no CaL spot had an encephalopathy panel analysis that reavealed two pathogenic variants in SCN1B and NF1.

Two patients with intellectual deficiency had a trio exome analysis. One is carrier of a frameshift variant in NAA15 inherited from the symptomatic mother. The second (a girl) is carrier of a pathogenic variant in HSD17B10 and a frameshift variant in CERT1. Metabolic work up is ongoing to evaluate the impact of the variant in HSD17B10 responsible for an X-linked mitochondrial dysfunction. The CERT1 variant is inherited from the symptomatic mother who also carries the NF1 variant. The mother has spina bifida, Arnold Chiari malformation, learning difficulties and one CaL spot.

Finally, two other patients had another diagnostic: Klinefelter syndrome and Greig cephalosyndactyly.

In conclusion, mild neurobehavioral symptoms are frequent in NF1. In our cohort, patients with additional phenotypes such as epilepsy or intellectual deficiency had NGS analysis and a second pathogenic variant was discovered in most of them. Therefore, we think that NGS analysis is recommended in patients with NF1 and atypical symptoms





14h30 - A CHALLENGING DIAGNOSIS UNVEILS POTENTIAL ADDITIONAL FEATURES OF MENKE-HENNEKAM SYNDROME

Presenting author: Eleonora Orlandini

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Menke-Hennekam syndrome-1 (MKHK1) (MIM #618332) is a recently defined monogenic condition caused by heterozygous variants in exons 30 and 31 of *CREBBP*. The core phenotype is characterized by intellectual disability (ID), microcephaly, short stature and feeding difficulties. Dysmorphic features, which differ from Rubinstein-Taybi syndrome (RSTS), appear heterogeneous and correlated to the genotype.

We describe the case of a male patient, the only child of healthy unrelated patients, born at term after unremarkable pregnancy. Prenatal growth retardation was evident at birth (weight -2.77 SDS), along with talipes equinovarus, cryptorchidism and atrial septal defect. He has always been suffering from feeding difficulties. He sat unsupported at 9 months and walked at 26 months; brain MRI revealed polymicrogyria of the right Rolandic operculum. Currently he is 15 years old and displays severe intellectual disability with absent speech and self-injurious behaviour (skin-picking). Because of short stature (-3 SDS) with partial GH deficiency, GH therapy was started at the age of 4, but discontinued because of poor response. IGF-1 levels remained low also during therapy; *GHR* mutations were excluded. From the age of 10 he started to exhibit mild fasting and post-prandial hyperglycemia, in absence of insulin resistance and autoimmunity.

Dysmorphic features were observed (Fig. 1) including microcephaly, telecanthus, short and upslanting palpebral fissures, depressed nasal ridge, long philtrum, micrognathia, large cupshaped ears, bilateral pes cavus with fibular deviation of the distal phalanx of the halluces.

Karyotype, chromosomal microarray, polymicrogyria multigene panel and singleton whole exome sequencing were performed, resulting negative. Trio whole genome sequencing identified the missense variant c.5602C>T (p.Arg1868Trp) in *CREBBP*, previously described in six patients affected by MKHK1.

Compared to reported patients with variants between 5,595 bp and 5,614 bp, our case displays strikingly similar dysmorphic features, supporting the evidence of a highly recognisable facial phenotype. Also, the grade of ID is consistent with reports of patients carrying the same variant, suggesting a correlation between genotype and severe neurological impairment. However, polymicrogyria, as other cortical malformations, has never been described in MKHK and may contribute in this case to the severity of the phenotype.







In our patient, investigations for short stature revealed GH deficiency; suboptimal response to GH therapy must be interpreted considering also undernutrition. From late childhood, mild hyperglycaemia has been detected; these features have never been reported in previous MKHK cohorts.

In conclusion, we present a new case of MKHK1. Clinical and facial phenotype are consistent with previous reports; we describe for the first time an association with additional neurologic and endocrine features. Further studies are warranted to confirm these findings.

14h42 - CLINICAL PRESENTATION IN THE FIRST AFRICAN PATIENT WITH GREIG CEPHALOPOLYSYNDACTYLY CONTIGUOUS GENE SYNDROME (GPS-CGS) DUE TO DE NOVO DELETION OF 6 MB ON CHROMOSOME 7P14.1-P12.3, ASSOCIATED WITH SICKLE CELL ANEMIA

Presenting author: Prince Makay

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Greig cephalopolysyndactyly syndrome is an autosomal dominant genetic disorder characterized by macrocephaly, hypertelorism, variable syndactyly and pre- and postaxial polydactyly. Abnormalities of the corpus callosum may be associated. Chromosomal deletions (>1 Mb) that include the *GLI3* gene are referred to as Greig Cephalopolysyndactyly Contiguous Gene Syndrome (GPS-CGS), and the clinical presentation is more severe than the GCPS, including complex neurobehavioral disorders with intellectual deficiency, severe motor delay and neurological features.

We report the first phenotypic description of GPS-CGS in a patient from Central Africa.

A 7-year-old girl, born at term by normal vaginal delivery following an uneventful pregnancy. She is the fourth of six children born to healthy and unrelated young Congolese parents. She presented multiple episodes of fever and anemia during which she received blood transfusion 3 times. Before the age of 1 year, she underwent a surgical procedure for ablation of foot preaxial polydactyly and an anal bud. Her development was delayed regarding the gross and fine motor development (walked at 4-year-old) and her speech and language development remain delayed (stop language since 1-year-old). She presents hand stereotypies and has not acquired the hygiene autonomy. At 6 years she was treated for Pott's disease after a thoracic X-ray showed a pronounced thoracic kyphosis. Dysmorphism evaluation revealed macrocephaly, arched eyebrows, hypertelorism, epicanthus, convergent







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strabismus, broad nose, short columella, thick lips, big central incisors, short neck, pointed chin, small umbilical hernia, camptodactyly of 5th fingers, hands postaxial polydactyly, feet preaxial polydactyly, toes camptodactyly 2-3 at right, toes partial syndactyly 1-5 at right, toes clinodactyly (3 and 4 at left, 4 and 5 at right), and bilateral overlapping toes 2 to 3.

Trio-based Whole Genome Sequencing identified a 5.84 Mb *de novo* deletion on chromosome 7p14.1-p12.3, classified as pathogenic. Also we incidentally found that she was homozygous for the classical Sickle Cell Anemia mutation in the *HBB* gene [NM 000518.4:c.20A>T(p.Glu7Val)], either parent being heterozygous.

This 7p14 deletion encompassing the *GLI3* gene results in functional haploinsufficiency of *GLI3* gene and is associated with GPS-CGS. This is consistent with the clinical phenotype in our patient compared to those described in the literature. The severity of the phenotype is caused by deletion of contiguous genes. The medical history of blood transfusion is consistent with the sickle cell anemia incidentally identified in WGS analysis.

Keywords: Greig Cephalopolysyndactyly Contiguous Gene Syndrome; Greig cephalopolysyndactyly syndrome; *GLI3*; Dysmorphism; Central Africa

14h54 - NOVEL LOSS-OF-FUNCTION STAG1 VARIANT IN A PATIENT WITH CENTRAL PRECOCIOUS PUBERTY AND SYNDROMIC NEURODEVELOPMENTAL DISORDER

Presenting author: Ioana Streata

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BACKGROUND Phenotypes for newly described gene-disease associations often undergo rapid evolution as additional cases are described. The expansion of exome and genome sequencing has contributed to this phenomenon by allowing ascertainment of diseases based on genotype rather than phenotype. We describe an example of phenotype expansion for the *STAG1* gene, which encodes a subunit of the cohesin complex, with an essential role in chromosome segregation during cell division, gene transcription, DNA repair and replication. *STAG1* gene has been implicated in a severe autosomal dominant neurodegenerative disorder, known as "Intellectual developmental disorder, autosomal dominant 47" (OMIM # 617635), which includes microcephaly, feeding difficulties, joint hyperlaxity, cognitive impairment, cerebral atrophy and seizures. We describe a newly diagnosed case with central precocious puberty not previously associated with the disorder.

CASE PRESENTATION The proband is a 8 year- and 5 month-old Romanian girl born to healthy, non-consanguineous parents. There was no family history of known congenital







anomalies, genetic disorders, epilepsy, or intellectual disability. She was born after a normal full-term pregnancy, with a birth weight of 3,200 g (10th centile) and length of 50 cm (25th centile). Occipitofrontal circumference (OFC) was not reported. There were no remarkable events during the perinatal period. Her developmental milestones were not severe delayed. In addition, the parents reported frequent respiratory tract infections, puberty onset at 5 year- and 6 month-old and anxiety. On physical examination at 8 years old, her height was 138.5 cm, weight was 48.5 kg (50–75th percentile), with a BMI of 25.3 kg/m2 specific for overweight. Her dysmorphic facial features included relative microcephaly, a prominent forehead, deep set eyes, sinofris, bulbous nose, short neck, hypertrichosis (legs and paravertebral), low posterior hair insertion, hands with fusiform fingers and feet brachydactyly. Electroencephalography (EEG), electrocardiogram and echocardiogram were unremarkable as well as vision and hearing evaluations resulted both normal.

CONCLUSIONS Our paper provides a detailed clinical presentation of a girl affected with autosomal dominant Mental retardation type 47 (MRT47, OMIM 617635) and expands the mutational spectrum associated with this extremely rare genetic condition. This is the first case of MRT47 identified in Romania.

15h06 - FOCAL DERMAL HYPOPLASIA IN PATIENT WITH MOLECULAR VARIANT IN GNAS GENE

Presenting author: Dorota Wicher

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A 2-year-old girl with coarctation of aorta and slightly delayed psychomotor development was referred to a geneticist due to suspicion of Goltz syndrome.

The first skin changes were observed at 8 months of age in the umbilical region. The next lesions appeared on the left calf and on the back. They were described as diffuse, bluish, patchy, resembling flat hemangiomas. According to a dermatologic opinion they could result from insufficient blood supply due to aortic coarctation. A skin biopsy was performed twice and the histopathological examination revealed elastic fibers reduction. Due to the atrophy of the dermis, Goltz syndrome was suspected.

Exome sequencing was performed. DNA from the patient's blood and fibroblasts as well as DNA from the blood of her parents and brother were analyzed. There were no changes in the *PORCN* gene associated with focal dermal hypoplasia (Goltz syndrome). Instead, a *de novo* molecular variant c.1A>G, p.(Met1Val) in *GNAS* gene was detected. This nucleotide substitution changes the initiation codon methionine (ATG) to valine (GTG) and blocks initiation of translation. It was described previously in patient with Albright hereditary osteodystrophy (Patten et al., 1990).







GNAS is a complex transcriptional unit with multiple transcript variants through the use of alternative first exons, alternative splicing of downstream exons, antisense transcripts, and reciprocal imprinting. Disorders associated with GNAS inactivation include pseudohypoparathyroidism Ia, Ib, and Ic (PHP-Ia, -Ib, -Ic), pseudopseudohypoparathyroidism (PPHP), progressive osseous heteroplasia (POH), and osteoma cutis (OC). In addition phenotype depends on parental origin of GNAS mutation.

Our patient was assessed for symptoms related to these disorders.

Clinical examination revealed short stature, round face and mild shortening of fourth metacarpals. No signs of heterotopic ossification of the dermis and subcutaneous tissues were found. Laboratory findings included mild elevation of alkaline phosphatase, low IGFBP3 and low nocturnal growth hormone (GH) secretion. GH stimulating tests are planned.

Because PHP is usually detectable later in life (the average age of diagnosis is 7 years for PHP-Ia and 10-12 years for PHP-Ib) the follow-up is necessary.

Regarding the dermatological symptoms, there are some publications on skin changes in patients with GNAS-related disorders. Klaassens et al. described male patient with Albright hereditary osteodystrophy (AHO) caused by the same molecular variant as in our patient. Part of his skin changes had an atrophic appearance with reddish translucency, however no skin biopsy was available. Lau et al. reported an infant with disseminated atrophic skin lesions and paternally inherited PPHP, who subsequently developed extensive cutaneous calcification.

Our case confirms that mutated GNAS gene can lead to skin atrophy.

Interpretation of genotype-phenotype correlation in *GNAS*-dependent disorders might be challenging in young presymptomatic patients.

15h18 - RENAL ANOMALIES, THROMBOCYTOPENIA AND MULTIPLE BONE CYSTS IN A PATIENT WITH NONO ASSOCIATED X-LINKED INTELLECTUAL DISABILITY SYNDROME

Presenting author: Karin Writzl

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The NONO gene encodes a nuclear protein involved in transcriptional regulation, RNA synthesis and DNA repair. Hemizygous loss-of function, *de novo* or maternally inherited variants in NONO have been associated with a recognisable X-linked intellectual disability syndrome (OMIM # 300967), characterized by developmental delay, intellectual disability, hypotonia, macrocephaly, elongated face, structural abnormalities of corpus callosum







and/or cerebellum, congenital heart defect and left ventricular non-compaction cardiomyopathy. To date, only a dozen patients have been described in the literature and the phenotype data are limited.

We report a 17- year-old boy with macrocephaly, elongated face, strabismus, speech and motor delay, intellectual disability, congenital heart defect (ASD, VSD and Ebstein's anomaly), left ventricular non-compaction cardiomyopathy, bilateral inguinal hernia and cryptorchidism. Additional features included renal anomalies (bilateral dysplastic kidneys), thrombocytopenia, and multiple bone cysts detected after left forearm fracture and located in the distal left radius, proximal left fibula and tibia, and distal left femur. Exome sequencing revealed a *de novo* pathogenic variant (NM_001145408.2: c.348+2_348+15delTGAGCAAC TGTTGG) in intron 5 of the *NONO* gene.

Renal anomalies and thrombocytopenia have each been reported in one patient with NONO - X-linked intellectual disability syndrome, while multiple bone cysts have not previously been associated with this syndrome. The phenotypic spectrum of NONO - X-linked intellectual disability syndrome may be broader than currently known.

15h30 - EXTENDING THE PHENOTYPIC SPECTRUM OF BAINBRIDGE-ROPERS SYNDROME

Presenting author: Stephanie Van de Voorde

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Background: 16-year-old girl with developmental delay, first child of non-consanguineous couple of northern European origin. She was born at 37 weeks of gestation following an uncomplicated pregnancy. Neonatal hypotonia, feeding difficulties and dysmorphic features such as microcephaly, facial asymmetry and absent fifth toenails were present at birth. Over the years, she has been diagnosed with severe developmental delay, seizures and absent speech. Genetic testing did not confirm several possible clinical diagnoses. Clinical assessment at 16 years showed sparse hair, long face, high forehead, hypertelorism, tubular nose, low-hanging columella, prominent glabella, bushy arched eyebrows with medial flaring, mild synophrys, high narrow palate, crowded teeth, thick and everted lower lip, elbow and lumbar hypertrichosis, kyphoscoliosis, and small and dysplastic fifth toenails. Some of her features were suggestive of Coffin-Siris Syndrome and further extended genetic testing was discussed with the parents.

Methods and Result: Mendeliome trio-analysis was performed according to standard procedures. Clinical exome testing detected a pathogenic frameshift variant in the *ASXL3* gene NM_030632.3(ASXL3):c.1346dup. This variant, to our knowledge, has not yet been reported in the literature.







Discussion: Bainbridge-Ropers syndrome (BRPS) is a rare genetic condition, caused by *de novo ASXL3* gene pathogenic variants. Affected children have neurodevelopmental delay with no or limited speech, hypotonia, feeding difficulties, behavioral problems and seizures. Dysmorphic facial features, such as long face, hypertelorism, down slanting palpebral fissures, synophrys, tubular nose with prominent nasal bridge, low-hanging columella, higharched and narrow palate, dental anomalies and micrognathia are reported in majority of affected individuals. Skeletal abnormalities are also common. However, hypertrichosis and fifth-digit nail hypoplasia have not been frequently reported in the literature. In the present patient, the detected *ASXL3* variant is a novel *de novo* pathogenic frameshift variant predicted to generate a premature stop codon. Other *ASXL3* pathogenic frameshift variants have previously been reported in BRPS patients.

Conclusion: We present a BRPS patient with distinctive clinical features that demonstrate partial overlap of the extended BRPS phenotype with other rare genetic syndromes such as Coffin-Siris syndrome.

15h42 - ZNF148 HAPLOINSUFFICIENCY IN A PATIENT WITH INTELLECTUAL DISABILITY AND OSTEOPOROSIS

Presenting author: Maria Isis Atallah Gonzalez

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Introduction: Zing finger proteins are a group of proteins that regulate gene expression. Truncating mutations in *ZNF148 (OMIM*601897)* was previously described in four patients (aged 0 to 11.7 years) with intellectual deficiency (ID), corpus callosum defects, short stature and facial dysmorphism. In this case report, we report an additional older patient and the only one with osteoporosis.

Case report: A 36-year old woman with moderate ID and osteoporosis was referred for genetic investigation. She was born at 40 weeks with normal growth parameters and presented transient respiratory insufficiency and severe feeding problems. She presented



development delay and she received special need education. She had strabismus, conductive hearing loss due to recurrent otitis, severe constipation, severe scoliosis and autistic traits. At age 13, bone age radiography showed bone demineralization. At adulthood, she presented several

THACA

stress-osteoporotic fractures (feet and tibia) and dexa scan showed a Z-score of -3.7.

At clinical examination, we observed a short stature 148.5 cm (P<3), microcephaly 50 cm (-4.1 DS), short 4th-5th toes of the left foot and some facial dysmorphic features. (Fig. 1A)

Fig.1 A. Facial dysmorphism evolving with age: straight eyebrows, low columnella, smooth piltrum, pointed chin and prognathism; B. Structure of the *ZNF148* gene and location of pathogenic variants.

Whole Exome Sequencing targeted on 1832 genes implicated on developmental disorders revealed a "de novo"

heterozygous variant in *ZNF148* [c.1371dupA,(p.ValCysfs*3)] (Fig. 1B). No pathogenic variant was observed among the 76 tested genes in the bone fragility panel.

Discussion: This case report expands the phenotypic profile of *ZNF148* ID and suggests that some skeletal features such as scoliosis and bone fragility could also be part of the phenotype.

15h54 - NOVEL HETEROZYGOUS MISSENSE MUTATION IN THE SKI GENE RELATED SHPRINTZEN- GOLDBERG SYNDROME: A RARE ADULT PATIENT

Presenting author: Gokcen Karamik

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Shprintzen-Goldberg Syndrome (SGS, OMIM #182212) is a rare multisystemic connective tissue disorder with AD inheritance caused by mutation in the SKI gene. We present a case diagnosed as SGS, followed up since childhood. A 23-year-old female patient was first evaluated in the pediatric genetics department when she was 10 years old because of marfanoid habitus. There was a history of birth as 2250 gr weight, 52 cm height. The prenatal screening was normal. There was a history of closure of the anterior fontanel before six months. Familial consanquinity and history were negative. The weight and height were 63 kg,180 cm respectively. The overarm length was 185 cm, and the upper/lower segment ratio was 0.8. She had an asthenic appearance, pectus carinatum deformity, scoliosis, arachnodactyly, genu valgum, hallux valgus deformity, pes planus, hyperelastic skin and decrease in subcutaneous fat tissue. There was a 1/6 systolic murmur. Dysmorphic facial features were round face, hypertelorism, wide nasal root, ocular proptosis, maxillary hypoplasia, microretrognathia, low soft ear, and upturned nose. Keratoconus and high-grade astigmatism were detected, unilateral hearing loss developed and she started using a hearing aid. She had balance problems and foot pains and described difficulty in breathing, and heart palpitations. Basal metabolic tests profile were normal. Echocardiography showed mitral valve prolapse and mitral insufficiency. Propafenone hydrochloride treatment was started because of sinus tachycardia in Holter electrocardiography. The pulmonary function test and thorax CT were normal. X-ray images showed kyphoscoliosis, genu valgum, and







hallux valgus deformity. Karyotype analysis was reported as 46, XX. No pathogenic variant was detected in the FBN1 gene analysis. WES analysis revealed a heterozygous novel missense mutation in the SKI gene (NM 003036.4) c.383 A>G (p.Asn128Ser). The mutation was located in the R-SMAD domain of the gene in exon 1. It has been shown to be pathogenic by in-silico prediction programs, it was classified as a variant of VUS according to the ACMG criteria. The variant was not previously reported in Clinvar, gnomAD, and literature. SGS was first described in 1982, there are less than 100 cases reported in the literature. The main findings of the syndrome are craniosynostosis and marfanoid appearance. Musculoskeletal and cardiovascular system anomalies, prominent craniofacial features are seen. Dolichocephaly, hypertelorism, proptosis, microretrognathia, low posteriorly located ear are dysmorphic facial features. Hypotonia, intellectual disability, ocular findings, brain anomalies, hernias are the other clinical signs. Mutations in the SKI gene cause dysregulated signaling of transforming growth factor-beta (TGFβ). R-SMAD domain is defined as hotspot region. Here, we aimed to present the dysmorphic features, clinical and molecular data of this syndrome, which is rarely seen in adults, in the light of the literature.

16h45 – SESSION 10: CYTOGENETICS (Chair: Ausra Matuleviciene)

16h45 - TOWARDS A EUROPEAN CONSENSUS GUIDELINE FOR PHELAN-MCDERMID SYNDROME

Presenting author: Conny M. A. van Ravenswaaij-Arts

<u>Conny M. A. van Ravenswaaij-Arts</u>^{1,2} on behalf of the European Phelan-McDermid syndrome consortium

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On October 22nd, 2020, the Phelan-McDermid syndrome (PMS) awareness day, the European PMS consortium had its first meeting to establish a PMS consensus guideline. In June 2022 the consortium will have a final consensus meeting and presenting the methods used to develop the guideline at the EuroDysmorpho meeting will be part of its implementation.

In 2018, a Dutch guideline on PMS was accredited and became online available in the Dutch guideline registry. This guideline was developed using the AGREE II and GRADE instruments. The same instruments, as well as a translated version of the Dutch guideline formed a starting point for the European guideline.

A European consortium was formed consisting of professionals and patient representatives. The 60 professionals consisted of clinical, behavioural and laboratory specialists, as well as







researchers, representing 15 different countries. Patient representatives were recruited by contacting all European patient organisations listed in Orphanet as being involved in PMS. This resulted in twelve patient representatives from six countries actively involved in writing the guideline. The consortium was organisationally supported by ERN-ITHACA.

Subsequently, a world-wide multi-lingual survey was developed for parents in order to find out what were the most important problems they experienced and how the care around their child was organised. Fundamental questions were formulated and working groups were formed to answer these per topic: definition of the syndrome; communication; gastrointestinal; sensory; epilepsy; sleep; lymphedema; mental health; genetic counselling; and organisation of care. A patient representative was part of each working group.

The working groups addressed the fundamental questions by literature review and expert opinions in order to arrive to recommendations. Each topic chapter was reviewed by the complete consortium and all recommendations were discussed plenary at the almost monthly online meetings of the consortium.

In June 2022, the final version of the guideline will be discussed at a physical consensus meeting. Next steps are focussed on implementation: publication of the complete guideline, a short practical version for clinicians and a lay version in all European languages for families.

17h00 - PARENTAL PERSPECTIVES ON PHELAN-MCDERMID SYNDROME; THE RESULTS OF A WORLDWIDE SURVEY

Presenting author: Sylvia A. Koza

Sylvia A. KOZA1, Annemiek M. LANDLUST1,2, Conny M.A. VAN RAVENSWAAIJ-ARTS1,2 on behalf of the European Phelan-McDermid syndrome consortium

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Phelan-McDermid syndrome (PMS; OMIM #606232) is a rare neurodevelopmental disorder caused by 22q13 deletions or pathogenic variants of SHANK3. It is characterized by hypotonia, developmental delay, absent or delayed speech, minor dysmorphic features, and autism spectrum disorder. Currently, evidence-based recommendations for the care of PMS patients are scarce, and for this purpose, a European consortium is developing a guideline. An indispensable part of this guideline is knowledge of the needs of parents.

We developed an online, multi-lingual survey for parents of individuals with PMS, which included questions on experienced problems, knowledge of the genetic cause, level of care, and communication between care providers. We analyzed the answers per age group, genotype, and continent of origin with chi-square tests, including posthoc analysis.







We received 587 answers from 35 countries representing every continent. Parents most frequently experienced problems with speech and communication (96%), learning difficulties/intellectual disability (94%), problems with fine motor skills (82%), altered pain perception (77%), and hypotonia (76%). At least one behavioral problem was present in 90% of individuals, and at least one problem occurring later in life in 64%. Adults had significantly higher rates of sleeping problems, regression, psychiatric problems, and epilepsy compared to one or more of the other age groups. Individuals with 22q13 deletions (n = 200) had significantly higher rates of hypotonia, lymphedema, problems with gross motor skills, teeth, kidneys, and heart, while individuals with SHANK3 mutations (n = 58) had significantly higher rates of mood problems, aggression, and severe psychiatric problems. Fewer parents from South America experienced always organized communication, were informed about the genotype of their child and received care at an academic hospital compared to parents in other continents.

Parents reported various developmental, neurological, behavioral, and other clinical problems in individuals with PMS, and most were present in all age groups and genetic backgrounds. Adult patients may have additional care needs as the prevalence of some problems increases with age. The genetic background influences the phenotype, as individuals with SHANK3 mutations seem to have higher rates of behavioral and psychiatric problems. The differences among countries are crucial to consider in an international guideline.

17h15 - UNRAVELLING THE PHENOTYPIC SPECTRUM OF TERMINAL 6Q DELETIONS WITH THE HELP OF SOCIAL MEDIA – A PROMINENT ROLE FOR DLL1

Presenting author: Aafke ENGWERDA

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Chromosome 6 aberrations are rare, and parents of children with such an aberration often search the internet and unite in international social media platforms. The Chromosome 6 Project is a collaboration between the University Medical Centre Groningen and a Chromosome 6 support group on Facebook. We aim to improve the surveillance of patients with chromosome 6 aberrations and the support of their families by increasing the available information on these rare aberrations.

Here we present our data on 93 individuals with terminal 6q deletions and 11 individuals with interstitial 6q26q27 deletions, including 38 newly identified individuals. Families signed up for the study via the secured project's website by uploading the proband's array report.







Phenotype data was collected directly from parents via a multilingual online questionnaire. Literature case reports were added to the database using the same questionnaire.

The terminal 6q26q27 region encompasses eight genes which are predicted to exhibit a haploinsufficiency effect (MAP3K4, PRKN, QKI, PDE10A, AFDN, DLL1, PSMB1 and TBP). We analysed the clinical data of the total group of individuals and of subgroups based on the number of deleted haploinsufficiency genes.

A common, but highly variable terminal 6q deletion phenotype could be identified, including microcephaly, vision problems, feeding problems, respiratory problems, spinal cord abnormalities, abnormal vertebrae, scoliosis, joint hypermobility, brain abnormalities (ventriculomegaly/hydrocephaly, corpus callosum abnormality and cortical dysplasia), seizures, hypotonia, ataxia, torticollis, balance problems, developmental delay, sleeping problems and hyperactivity. Other clinical characteristics often reported were congenital heart defects, kidney problems, abnormalities of the female genitalia, spina bifida, anal abnormalities, positional foot deformities, hypertonia and self-harming behaviour.

Subgroup analysis learned that phenotypes were comparable up to a deletion size of 7.1 Mb and most features could be attributed to the terminally located gene DLL1. Individuals with interstitial deletions including DLL1 presented with the same phenotype. Larger deletions including QKI (>7.1 Mb) lead to a more severe phenotype including additional clinical characteristics.

Our study shows that social media helps in collecting detailed genotype-phenotype data from large numbers of patients with rare chromosome aberrations, which enables a more precise description of the phenotypicspectrum

17h30 - THE PHENOTYPIC SPECTRUM OF TERMINAL AND SUBTERMINAL 6P DELETIONS BASED ON A SOCIAL MEDIA-DERIVED COHORT AND LITERATURE REVIEW

Presenting author: Eleana Rraku

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Chromosome 6 disorders are rare, and information on their clinical consequences is scarce. This impedes optimal management by clinicians and causes great uncertainty for parents of affected children. To improve this, the Chromosome 6 Project collaborates with families of affected individuals worldwide through social media platforms. Here, we present our findings on 13 newly identified individuals and 46 literature cases with terminal and interstitial 6p25 deletions.







Parents were notified of the study through social media and were requested to upload an official microarray report in order to participate. Phenotype information was collected directly from families through a multilingual web-based questionnaire, which was also used to extract the information from the literature cases. Phenotype descriptions were made for the whole group and for six subgroups based on deletion sizes.

The total group shared a common phenotype characterized by ocular anterior segment dysgenesis, vision problems, hearing impairment, cardiac defects, brain abnormalities, dysmorphic features and mild developmental delay. These characteristics can be largely attributed to the haploinsufficiency of FOXC1, one of the most distally deleted genes. Kidney abnormalities, complex heart defects and corpus callosum abnormalities were more commonly seen in individuals with larger deletions, some of which might be explained by the loss of other genes in the 6p25 region (RREB1 in cardiac phenotypes and TUBB2B in the corpus callosum abnormalities).

By collecting information directly from families, we uncovered a number of previously unreported features, including neonatal and gastrointestinal problems, sleep disturbances and behavioural characteristics. Our observations enabled us to provide recommendations for clinical surveillance.

17h45 - NOVEL MOLECULAR CAUSE OR JUST A COINCIDENCE? 6P25 DUPLICATION INVOLVING FOXC1 MAY BE ASSOCIATED WITH BRACHYDACTYLY TYPE

Presenting author: Naz Guleray Lafcı

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Brachydactyly type E (BDE) is characterized by variable shortening of the metacarpals and/or metatarsals. The molecular etiology is heterogeneous and partially characterized. BDE may appear as an isolated finding or represent a syndromic manifestation. In this study, we report 3 affected individuals with BDE harboring 6p25 duplications involving *FOXC1*.

<u>Individual 1:</u> She was referred for short stature and obesity. Physical examination at the age of 12 years revealed a height of 128.6 cm (-3.81 SD), a weight of 41.25 kg (-0.49 SD) and a head circumference of 51.5 cm (-1.78 SD). She had high anterior hairline, prominent forehead, round face with malar hypoplasia, bulbous nasal tip and full lips. She also had bilateral brachymetacarpia of 4th fingers and brachymetatarsia of 4th toes compatible with







the diagnosis of BDE1. Renal ultrasound demonstrated multicystic dysplastic kidney. Initially, her appearance was suggestive of pseudohypoparathyroidism, but sequencing along with MLPA analysis for both methylation and copy number status of *GNAS* resulted in normal. Furthermore, sequencing of the other genes associated with BDE including *HOXD13*, *PTHLH*, *PDE3A* and *SHOX* was normal.

Individual 2: She was born to non-consanguineous parents at term. Anthropometric measurements at the age of 8^{3/12} years revealed a height of 122 cm (-1.16 SD), a weight of 23 kg (-0.88 SD) and a head circumference of 49 cm (-2 SD). She had similar facial dysmorphism as the individual 1, except for long face and thin lips. Skeletal survey demonstrated bilateral brachymetacarpia of 4th and 5th fingers, along with bilateral brachymesophalangia of 2nd and 5th digits. During her follow-up, hypertension developed. Her mother was also affected with bilateral short 5th metacarpals, Madelung deformity and short stature. BDE in combination with hypertension raised the suspicion of "Hypertension and Brachydactyly Syndrome", but *PDE3A* sequencing was normal.

Individuals were screened for copy number variations and analysis revealed duplications of 1.5 Mb and 8,1 Mb on chromosome 6p25, respectively. Three OMIM genes attributed to a disorder including *FOXC1* were common in both duplications. *FOXC1* is a well-known transcription factor involved in the etiopathogenesis of Axenfeld Rieger syndrome (ARS). Intriguingly, the hallmark feature of ARS that is ocular abnormalities were not observed in the affected individuals. Furthermore, *FOXC1* is required for IHH-Gli2 regulated endochondral ossification and even though brachydactyly is not a constant finding in all previous cases harboring overlapping 6p25 duplications in the literature, there are 3 more individuals reported with brachydactyly to the best of our knowledge. The occurrence of brachydactyly may be due to an increased gene dosage or topographical change of 3D genome architecture, as *FOXC1* lies just adjacent to the overlapping duplicated region. We postulate that 6p25 duplications involving *FOXC1* could be another underlying molecular cause of BDE.

18h00 - 22Q13 MICRODUPLICATION SYNDROME IN THREE PATIENTS RESULTING FROM PARENTAL CHROMOSOME 22 PERCENTRIC INVERSION

Pezsenting author: Katalin Szakszon

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Distal duplication 22q (22q13.3qter) is a rare condition with less than 30 cases described so far. The clinical phenotype of patients is highly variable and does not always correlate with the extent of the duplicated segment. Short stature, microcephaly, hypertelorism, cleft lip or palate, low-set ears, and intellectual disability seem to be the most consistent features. Familial reoccurrence is extremely rarely reported. Parental balanced reciprocal translocations and pericentric inversions involving chromosome 22 may serve as a basis for the conception of an unbalanced offspring and are more frequently reported than de novo events.

Here, we report two siblings with a 22q13.3qter duplication detected by array CGH; whose relatively mild phenotype and identical chromosomal breakpoints are quite unique and whose mother is a carrier of a pericentric inversion of chromosome 22. In addition, an unrelated boy is described with a larger duplicated segment spanning from 22q13.1 to 22qter, presenting with a more severe phenotype, habitual spontaneous abortions in the family history, whose aneusomy was attributed to paternal pericentric inversion of chromosome 22.

Our case reports with supporting cyto- and molecular cytogenetic data expand the phenotypic spectrum of 22q13 duplication syndrome and highlight the mechanism by which a rearranged form of the inverted chromosome 22 may be passed on to the offspring after meiotic recombination and result in an unbalanced conceptus.

18h15 - FURTHER DELINEATION OF THE HIDEA SYNDROME

Presenting author: Elisa Rahikkala

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HIDEA syndrome (hypotonia, hypoventilation, impaired intellectual development, dysautonomia, epilepsy, and eye abnormalities) (OMIM #618493) is a syndromic intellectual disability disorder caused by biallelic pathogenic variants in *P4HTM*. Here, we report six new HIDEA patients and review the clinical and molecular data of previously reported cases (N=23).

Common associated features are global developmental delay / intellectual disability N=27/27, 100%), hypotonia (N=28/29, 97%), strabismus (N=16/24, 67%) or other ophthalmological abnormalities (N=21/26, 81%), obesity (17/28, 61%), and epilepsy (N=17/29, 59%). Hypoventilation, sleep apneas, and respiratory tract infections in some HIDEA patients are also common indicating the importance of performing polysomnography and estimating the need for non-invasive ventilatory support.

We also delineate predictions of the crystal structure of all known *P4HTM* pathogenic variants, demonstrating that the disease associated-pathogenic variants are likely to disrupt P4H-TM activity. This report expands knowledge of the genotypic and phenotypic spectrum of the disease.

18h30 - NANCE-HORAN SYNDROME: AN ULTRA RARE PHENOTYPE DIGNOSED IN A FAMILY WITH FEMALE SIBLING AFFECTED AS SEVERE AS THE MALE

Presenting author: Sinem Kocagil

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Nance-Horan syndrome (OMIM #302350) is an ultra rare, X-linked disorder that is characterized by congenital cataracts, dental anomalies, dysmorphic features and intellectual disability. There have been around 30 families reported in the literature so far and the underlying gene has been identified as *NHS*. Here we report two siblings; a 15-year-old female and 20-year-old male, both were severely affected with classical findings of this rare phenotype.

15-year-old female patient was referred to our outpatients clinics for syndromic evaluation. She was born by normal spontaneous vaginal birth at 38th week of gestation with a birth weight around 2000 gr (<3p). She was diagnosed with bilateral congenital cataracts and had an operation at 2nd month of age and then 6 years of age. Her neuromotor development was delayed comparing to her peers. She was diagnosed with learning disability at 8 years of age and she started to have special education. Around age of 13, bilateral flexion contractures of knees were developed and she started to have difficulty in climbing stairs. Her cranial MRI showed hypoplastic midbrain and vermis hypoplasia. Parents of the proband were not related and it was learned that she had an older male sibling with similar







symptoms. In her physical examination; weight was 40 kg (-2,82SD), height was 165 cm (+0,52SD), head circumference was 55 cm (-0,46SD) and body-mass-index (BMI) was -4,04. She had long narrow face with high forehead, broad eyebrows, bilateral ptosis, prominent nasal bridge, multiple dental caries and abscent right lateral incisor, long slender extremities and arachnodactyly of the fingers and toes. Brother of the proband was born at 40th week of gestation with birthweight of 4000 gr. He had respiratory distress due to meconium aspiration and he has spent two hours in neonatal intensive care unit (NICU). His neuromotor developmental skills were delayed and he was diagnosed with bilateral cataracts around the age 3 and had operation. He had special education for learning disability. In his physical examination; weight was 60 kg (-0,5SD), height was 175 cm (+0,38SD), head circumference was 56 cm (-0,03SD) and body-mass-index (BMI) was -0,79. He also had long narrow face, broad eyebrows, long nose with prominent bridge and long slender extremities. Whole exome sequencing was performed at the proband and a novel heterozygous c.1241-4delC variant at NHS gene was detected. Sanger sequencing of the relevant variant at the affected brother revealed the variant as hemizygous state. In addition to that, segregation analysis was done by sanger sequencing at the unaffected mother and the variant was detected at her in heterozygous state similar to proband. Since the proband was female who were affected severely, further karyotype analysis and microarray analysis (Agilent, SNP array+Array CGH, 180K) for X chromosomal aberrations were done and revealed normal results. It was further planned to perform X-linked inactivation assay from the peripheral blood of the proband to identify possible skewed X inactivation. It is known that female patients are affected from the milder form of the syndrome and mostly opthalmological findings are seen. To our knowledge this is the first female patient in the literature with full clinical manifestation of this rare phenotype.

18h42 - THE PHENOTYPE AND THE DIAGNOSIS OF A NEW CASE OF MYHRE SYNDROME

Presenting author: Francesca Catapano

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Background: Myhre syndrome is a rare multisystemic autosomal dominant disorder characterized predominantly by short stature, facial dysmorphisms, skeletal signs, hearing







loss and potential involvement of cardiovascular, respiratory, gastrointestinal, and skin systems. Currently, only less than 100 cases have been described worldwide. The disease is caused by a spectrum of gain-of-function mutations in SMAD4 gene. Mutations in this gene result in an abnormality of TGF- β signalling which affects the development of several body systems and results in the Myhre syndrome specific phenotype.

Clinical Case: Our patient was born to non-consanguineous healthy Caucasian parents with unremarkable family history despite a father's cousin with trisomy 21. During the pregnancy Intrauterine Growth Restriction (IUGR) occurred at the beginning of the 3rd trimester in addition to absence of diastole flow on umbilical doppler, which is why the baby girl was born by emergency caesarean section at 29 weeks and four days of gestation. Her weight was 430g, the length was below the third percentile and Apgar score was 7-9. The little patient presented, in addition to prematurity, significant growth deficiency (already in the prenatal period), thyroid haemigenesis, 11 costal elements, joint limitations, spina bifida occulta (reported just in one other case) and dysmorphic features. Our patient was diagnosed with Myhre syndrome at the age of 23 months, which is very early for such a rare syndrome also comparing the diagnostic time of other patients reported in the literature, by a Next Generation Sequencing (NGS) panel of genes (that includes SMAD4 gene) that correlate with syndromic conditions characterized by growth deficits. The diagnosis was reached just before performing whole exome sequencing (WES) and after having performed CGH-array and panels for specific diseases (Silver-Russel, SHORT and Beckwith Wiedemann syndromes), all of which proved negative. Moreover, to our knowledge, hyposmia, thyroid haemiagenesis and microcrania have not been previously reported in this condition. Conclusion: We report the earliest diagnosis of Myhre syndrome, by NGS panel, as opposed to the other diagnoses obtained by WES. Early clinical diagnosis of Myhre syndrome in childhood is challenging because of the rarity of the condition itself and because early manifestations are less specific. A review of the literature highlights that the most frequent early signs are marked growth delay that continues into the postnatal period, musculoskeletal problems such as brachydactyly and muscle hypertrophy, hearing loss and intellectual disability. We recommend, in the presence of this symptomatology, to conduct an NGS panel that includes the gene SMAD4 in genetic diagnostics investigations. Moreover, we describe in our case the presence of new clinical signs that might be associated with Myhre syndrome and that should be considered in addressing the diagnostic suspicion.

18h54 - ANALYSIS OF A NEW CASE OF DELETION IN SHORT ARM OF CHROMOSOME 2

Presenting author: Giuseppe RAMACIERI

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Deletion of the short arm of chromosome 2 may be associated with different phenotypes but to date no specific clinical aspects were attributed to a deletion of 2p22.3. The purpose of this study was to investigate that region starting from the description of a new clinical case.

The patient was born at 37+5 weeks of gestational age from a spontaneous delivery. There was a prenatal diagnosis of bilateral pyelectasis. The newborn was transferred at birth to the Neonatal Intensive Care Unit due to an axial hypotonia and feeding problems. During the hospitalization he went through parenteral nutrition and a catheterism because of vescical retention. A subsequent cystography showed a III grade bilateral vescico-ureteral reflux. Echoencephalography, Brain Nuclear Magnetic Resonance, hearing and sight controls were normal. At hospital discharge the patient showed an improvement in feeding, starting eating solid food, and, even if his hypotonia was improved, he started a rehabilitative domiciliar therapy and a follow up by our ambulatory. At the last follow up visit, the patient was 14 months old; his weight was 9.37 kg (10°-50° percentile), length 79 cm (10°-50° percentile) and cranium circonference 49.5 cm (50°-90° percentile); he showed nystagmus, microretrognathia, telecanthus, horizontal palpebral fissures, thin upper lip, protruding columella, mild pectus excavatum and tight chest. He had a transient neutropenia but, to date, neutrophil level is in the normal range. He suffered from stipsis and frequent urinary infections due to the vescico-ureteral reflux. An echocardiography showed the presence of multiple interventricular defects lacking hemodynamic effects. The CGH-Array analysis showed a deletion of the short arm of chromosome 2 (del2p23.1p22.2), 6 Mb wide, and a triplication of 2p22.2.

To investigate the genetic cause of our patient's clinical condition we made a systematic bibliographic research on Pubmed, Database of Genomic Variants, ClinVar and Decipher of all clinical reports that included a deletion of 2p23.1p22.2 or triplication of 2p22.2. The triplication of 2p22.2 has no pathogenic relevance while the deletion of 2p23.2p22.2, or part of it, was reported as pathogenic in 17 cases.

Our patient shared with other 10 cases a deletion involving *CRIM1* gene, which is associated with growth factors implicated in motor neuron differentiation, and with 11 cases a deletion of both *FEZ2* region, a gene involved in axonal bundling and elongation within axon bundles, and the *VIT* gene, coding for a polysaccharide-binding protein of the extracellular matrix. All these cases showed neuromotor alteration that included a wide spectrum of malformations and symptoms, such as holoprosencephaly, axial hypotonia or mild development delay; these conditions can be associated with an alteration of the above-mentioned genes. Further analysis should be performed to understand any biological link between these genes and the clinical phenotype.





19h06 - BONE2GENE: ARTIFICIAL INTELLIGENCE-BASED RECOGNITION AND CLASSIFICATION OF GENETIC SKELETAL DYSMORPHISM

Presenting author: Behnam Javanmardi

Sebastian Rassmann¹, Kyra Skaf², Alexander Hustinx¹, Tzung-Chien Hsieh¹, Alexandra Keller³, Ruth Gausche⁴, Roland Pfäffle⁵, Martin Zenker², Klaus Mohnike², Peter Krawitz¹, <u>Behnam</u> Javanmardi^{1*}

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Introduction: With the rapid development of artificial intelligence and in particular deep learning (DL), various medical imaging modalities can be used for developing next-generation phenotyping tools that are able to detect and recognize various and subtle dysmorphisms and features caused by different genetic diseases. Rare skeletal disorders are an important group of genetic disorders that are highly heterogeneous, making their accurate diagnosis a very challenging process. In this project, we have (so far) collected more than 700 hand X-Ray images from patients diagnosed with 7 different skeletal disorders which we are using to build an Al-based diagnostic tool.

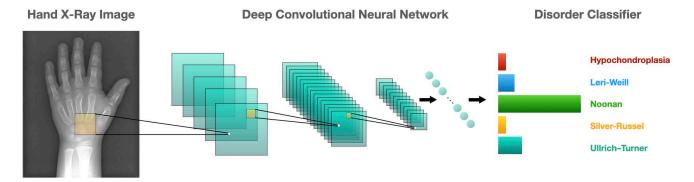
Method: DL usually requires massive amounts of training data. However, data for rare genetic disorders are inherently sparse, further exacerbated by difficulties collecting and digitizing existing X-Ray imagery. We address this issue by employing transfer learning from a public bone age dataset from the Radiological Society of North America (RSNA). Furthermore, varying data sources e.g. using differing imprinted labels or images showing digitization artifacts potentially induce biases. To eradicate these, we trained DL models to extract only the hands concealing the origin of the X-Ray.

Results: Our bone age DL models trained on the RSNA dataset reach a competitive accuracy with a mean absolute difference (MAD) of ~4.2 months (compared to 5-7 months from human experts). Furthermore, our models achieve a MAD of ~7.5 months (w.r.t. a single human rater) on our skeletal disorder dataset which demonstrates generalizability to unseen datasets and dysmorphic hands. Upon fine-tuning our models on disorder classification, we build a preliminary classifier. The current prediction accuracies widely depend on the class frequency in our dataset (3 - 72%). By growing our database we aim to improve the performance and, consequently, deploy Bone2Gene as a clinical assistance tool.









A schematic view of Bone2Gene. Visit bone2gene.com for more info.

DAY 4 – SATURDAY 17th of SEPTEMBER

09h00 – SESSION 11: SYNDROME DELINEATION CONTINUED (Chair: Sally Lynch)

09h00 - TAB2-RELATED SYNDROME: REPORT OF THREE NOVEL PATIENTS

Presenting author: Hendrica Belge

<u>Hendrica BELGE¹</u>, Wim WUYTS², Deniz KARADURMUS¹, Valérie BENOIT¹, Anne DESTREE¹.

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TAB2 encodes a scaffold protein, TAK1 binding protein 2, that acts as a coactivator of TGF-beta activated kinase 1 (TAK1/MAP3K7) mediating various biological functions including inflammatory response, proliferation/differentiation, angiogenesis as well as myocardial homeostasis.

Heterozygous pathogenic variants in *TAB2* were initially reported to cause nonsyndromic congenital heart defects, including valvular and cardiac outflow tract structural abnormalities. Recently, heterozygous *TAB2* variants have been associated with a rare multiple congenital anomalies syndrome characterized by heart defects (most often mitral valve disease and cardiomyopathy), short stature, skeletal and connective tissue anomalies







(mostly joint hypermobility), facial dysmorphism and sometimes developmental delay. To date, a limited number of cases have been reported in the litterature.

Here we report three additional patients from two families harboring novel frameshift variants in the *TAB2* gene. We describe the clinical and molecular data of the affected patients, and discuss the variable expressivity in comparison to the previously reported individuals. Our findings further delineate the phenotype of the newly recognized *TAB2*-related syndrome.

09h15 - NOVEL RBP4 VARIANT AND MATERNAL PARENT-OF-ORIGIN EFFECT IN A FAMILY WITH OCULAR BIRTH DEFECT

Presenting author: Ugo Sorrentino

<u>U. Sorrentino^{1*}</u>, A. Busciglio¹, Chiara Rigon², Daniela Zuccarello¹, Leonardo Salviati¹⁻²

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We report the case of an 8 years old male patient, first child of two consanguineous parents (first cousins) of Mauritanian ethnicity, affected with bilateral anophthalmia, alopecia and mild developmental delay. Family history was unremarkable except for a first cousin affected by alopecia. As a first line of molecular diagnosis, expanded clinical exome sequencing was performed. Early focus on homozygous and hemizygous regions did not reveal any candidate variant relatable to the patient's phenotype; variant filtering was therefore shifted more specifically towards the ocular phenotype of the patient, allowing for the identification of the heterozygous missense variant c.367T>C p.(Trp123Arg) in the *RBP4* gene (NM_006744.4). The variant has a MAF of 0%, affects a highly conserved residue, and prediction software (Polyphen, SIFT) classify it as possibly damaging. Segregation analysis showed that the variant was of maternal origin, and subsequent ophthalmologic examination of the proband's mother led to the discovery of a previously undiagnosed unilateral optic nerve coloboma.

Pathogenic mutations in *RBP4*, which codes for a 21 kD retinol binding protein, have been associated with a wide spectrum of ocular developmental abnormalities, including microanophthalmia, iris coloboma and retinal dystrophy, with different modes of transmission. In particular, micro-anophthalmia caused by mutations in the *RBP4* gene has been reported as an autosomal dominant trait characterized by incomplete penetrance and by variable expressivity. The phenotype is usually more severe in the case of maternal transmission of the pathogenic variant, due to an additive maternal-fetal effect of the retinol transport defect present in both mother and fetus (PMID: 25910211). Very few confirmed pathogenic *RBP4* variants have so far been reported in the literature.

The characteristics of the variant, the cosegregation of the genotype with the ocular disease in the family, and the presence of a much more severe phenotype in the child than in his affected mother, support a causative role of the p.(Trp123Arg) variant in the genesis of the







clinical manifestations in the proband (ACMG class 4). Further functional studies are required to validate such hypothesis.

09h30 - FURTHER DESCRIPTION OF THE PHENOTYPE CAUSED BY TRUNCATING VARIANTS IN SETD5 GENE

Presenting author: Yvan Herenger

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Introduction: Intellectual disability (ID) has an estimated prevalence of 2-3% and more than a thousand genes have been involved in neurodevelopmental disorders (NDD). Among these genes, *SETD5* is considered as a relative common form of ID associated gene and is associated with variable outcome and dysmorphic features.

Methods: We performed whole exome sequencing in 3 patients with NDD and identified 3 different truncating variants in *SETD5*. We describe the clinical and molecular data and review actual knowledges from the literature.

Results: In two patients with mild NDD, growth delay and suggestive facial features we identified two independent heterozygous frameshift-variant (p.(Ser1286Leufs*37), previously described, and p.(Leu990Phefs*20)). A third patient with severe NDD carry a previously undescribed nonsense variant (p.(Arg995*)). Based on these three patients we show a broad variability in the expression of *SETD5* associated NDD. An overlap with facial features from KBG syndrome is present in both patients with mild NDD, as previously reported.

Conclusion: Our cases report attests the broad spectrum of NDD in *SETD5* associated disorders and further defined the core facial dysmorphism.

09h45 - A NOVEL NONSENSE VARIANT IN RAB33B AS CAUSE OF SMITH-McCORT DYSPLASIA 2

Presenting author: Christina Roggia

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Smith-McCort dysplasia (SMC, OMIM #615222) is a very rare and disabling autosomal-recessive spondylo-epi-metaphyseal dysplasia with coarse facies, short trunk dwarfism with barrel-shaped chest and protuberant abdomen, kyphoscoliosis, genu valgum or varum, rhizomelic limb shortening and limited joint extensibility. Generalized platyspondyly with double-humped vertebral end plates and lace-like appearance of iliac crests are considered to be specific radiological features. Cognitive abilities are not impaired. The disorder is caused by mutations in either *DYM* or *RAB33B*, the latter coding for a GTP-binding protein involved in retrograde transport of Golgi vesicles and autophagy. So far only few individuals affected by *RAB33B*-related Smith-McCort dysplasia (SMC Type 2) have been described in the literature. We report an additional case of SMC type 2 due to a novel pathogenic stopmutation in *RAB33B*-gen.

A 29-year-old refugee from Palestine was referred to our department for genetic testing after external clinical diagnosis of osteogenesis imperfecta. He presented with short stature, chest deformity, short neck, genua valga and abnormal gait. He was not able to stretch his arms or close his fist. Prognathism and pes planus were also present. Radiological reports of chest and limbs were not available. He was the firstborn child to consanguineous parents (first-cousins). Both couples of grandparents were also consanguineous. His neuropsychological development was normal, but delayed height gain was noticed since the age of 2. Progressive bone deformities and painful joint stiffness appeared at the age of 15 years. Several fractures of fingers and arms occurred in the adolescence, always after traumatic events. Ocular, hearing or dental problems were denied. Blue sclera as a child could not be recalled. Currently, his chief complaint was severe hip joint pain not responsive to ibuprofen therapy. Body height was 140 cm, head circumference 54 cm and body weight 40 kg. Hematological and biochemical parameters were normal except for low vitamin D levels. All his seven siblings and his own three children were healthy and of normal stature according to age. Two of the patient's cousins show a similar clinical phenotype. Further clinical, radiological or genetic investigations in the family had never been performed.

Genome-sequencing of blood DNA revealed a homozygous pathogenic sequence variant, c.186_199delinsACGA, p.Glu63Argfs*51 in *RAB33B*, which was not present in an inhouse database as well as in gnomAD-Browser (gnomad.broadinstitute.org). Orthopedic and analgesic counselling were recommended. Our data support previous reports stating that phenotype of SMC type 2 seems to appear homogeneous regardless of the type of mutation in *RAB33B*.

10h00 - THREE NEW PATIENTS WITH VARIANTS IN CHD3 GENE

Presenting author: Amaia Lasa-Aranzasti

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Background/Objectives: Pathogenic variants in the *CHD3* gene have been associated with Snijders Blok-Campeau syndrome (OMIM 618205). To date, 61 patients have reported, mainly characterized by neurological involvement, dysmorphia and other characteristics such as hyperlaxity and visual disturbances among others. Although most variants identified appeared to be in protein's ATPase/helicase and C-Terminal domain, those that have been identified outside the domain, have not shown differences in the phenotype until now.

Methods: Here we report three patients from three unrelated families with heterozygous variants in the *CHD3* gene. In patients 1 and 2 the diagnosis was uncovered by whole-exome sequencing (WES) and in patients 3 by exome data reanalysis.

Results: WES identified c.3682C>T/p.(p.Arg1169Trp) and c.301_303delinsTC/ p.P101Sfs*6 variants in patients 1 and 2 and exome data reanalysis identified c.2951T>G/p.(Leu984Arg) variant in the third patient. c.3682C>T and c.2951T>G variants are located in ATPase and C-Terminal domains but c.301_303delinsTC variant is located outside and far from mentioned domains.

Common characteristics of the three patients include neurodevelopmental delay, delayed speech and language development, mild intellectual disability and some dysmorphic features such as macrocephaly, high forehead, hypertelorism, bifid nasal tip and thin upper lip.

Addionatlly, patient 2 showed naso-frontal encephalocele, gingival hyperkeratosis and pericallosal lipomas. The association of these findings have been described in Pai syndrome but not previously associated with *CHD3*.

Conclusions: A good clinical history and phenotyping can guide the diagnosis, mainly in recognizable entities such as Snijders Blok-Campeau syndrome. More patients should be described to elucidate whether the symptoms related to pai syndrome could be an extension of the phenotype described so far. It would also be interesting to see if there are more patients with variants in plant homeodomain or chromodomain domains and see if there could be a genotype-phenotype correlation.

Bibliography: 1° Drivas, Theodore G et al. "A second cohort of CHD3 patients expands the molecular mechanisms known to cause Snijders Blok-Campeau syndrome." *European journal of human genetics:* EJHG vol. 28,10 (2020): 1422-1431. doi:10.1038/s41431-020-0654-4, 2° Coursimault, Juliette et al. "Hypersociability associated with developmental delay, macrocephaly and facial dysmorphism points to CHD3 mutations." *European journal of medical genetics* vol. 64,4 (2021): 104166. doi:10.1016/j.ejmg.2021.104166 3° Mizukami, Miyako et al. "A de novo CHD3 variant in a child with intellectual disability, autism, joint laxity, and dysmorphisms." *Brain & development* vol. 43,4 (2021): 563-565. doi:10.1016/j.braindev.2020.12.004







10h15 - NEW VARIANTS CAUSING OKUR-CHUNG SYNDROME AND MACROCEPHALY

Presenting author: Alice PORTO VASCONCELOS

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Okur-Chung syndrome (MIM#617062) is a rare autosomal dominant disorder with less than 40 patients reported so far. This syndrome is known to cause neurodevelopmental disorder and variable dysmorphic features, growth retardation, immune deficiencies, gastrointestinal disorders and brain abnormalities, among other findings. Okur-Chung is caused by pathogenic loss-of-function variants in the *CSNK2A1* gene. We report two new caucasian patients with Okur-Chung syndrome and new likely pathogenic variants and features.

The first patient is a 14-year-old male born to non-consanguineous parents. He had acute adrenal crisis in the first month of life requiring high dose hydrocortisone and fludrocortisone, that recurred upon every reduction attempt. He was born with atrial septal defect with left-to-right shunt. He subsequently developed post-natal onset growth retardation, macrocephaly and moderate intellectual disability. The patient has short stature (below -2SD), mild facial dysmorphisms (including deep-set eyes, wide and depressed nasal bridge and anteverted nares) and persistent fetal fingertip pads. After brain and abdominal scans and analytical workup, an etiology for the adrenal insufficiency was not found. A copy number variation screening for the *CYP21A2* gene and NGS panel for genes related to Congenital Adrenal Hyperplasia that did not reveal possibly pathogenic variants. Afterwards, an array comparative genomic hybridization (CGH array) showed a deletion in band 20p13, encompassing 12 genes, among which the *CSNK2A1* gene. The other genes included in the deletion are not known to be related to genetic disease to date. The deletion was inherited from the father, also with short stature (-2SD) and history of learning difficulties.

The second patient is a 9-year-old born to non-consanguineous parents. He was born premature, at 35 weeks of gestation, and had neonatal respiratory distress. He presented hypotonia at birth and developed post-natal macrocephaly and intellectual disability. Physically he displays normal stature and mild dysmorphisms (including depressed nasal bridge and anteverted nares) and persistent fetal fingertip pads. Metabolic workup and brain imaging did not reveal any abnormalities. The CGH array did not show any possibly related variants and clinical exome sequencing through NGS revealed the heterozygous variant c.723+1dup r.(spl?) in *CSNK2A1* gene, classified as likely pathogenic. The parental study is still ongoing.

In conclusion, we report two novel variants causing Okur-Chung syndrome. Gross deletions have not been previously reported as a cause for the syndrome. As for splice-site variants, this is the third reported to date. Both patients share macrocephaly, unlike previously reported patients, and some dysmorphic features. Additionally, we include the first patient







with unexplained adrenal insufficiency. We propose these new patients can further expand the clinical spectrum of Okur-Chung syndrome.

11h00 - SESSION 12: SYNDROME DELINEATION CONTINUED (Chair: Conny van Ravenswaaij-Arts)

11h00 - DE NOVO SPLICING ZC4H2 VARIANT IN A PORTUGUESE FEMALE PATIENT WITH ARTHROGRYPOSIS MULTIPLEX CONGENITA

Presenting author: Diogo Fernandes da Rocha

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ZC4H2-Associated Rare Disorders (ZARD) are an X-linked Arthrogryposis Multiplex Congenita (AMC) disorder associated with a wide range of clinical features such as short stature, microcephaly, hypotonia, and broad neurodevelopmental delay. The spectrum of ZC4H2 defects comprises mostly missense variants in affected males, and de novo splicing, frameshift, nonsense, and partial deletions in affected females. Here we present a 17-yearold only girl born with claw hands, hypotonia, and posterior cleft palate with hydramnios in the prenatal period and neonatal respiratory distress due to laryngomalacia in the first days of life. At 2 years old, she underwent cleft palate and clubfoot correction. During childhood and adolescence, she was submitted to other orthopedic surgeries to reduce gait and fine motor limitations and ENT surgeries for recurrent episodes of acute otitis media that were affecting hearing ability. Currently she presents with bilateral distal arthrogryposis, bilateral camptodactyly of 2-5 fingers, obesity with high appetite, short stature, non-progressive scoliosis, hypotonia with poor posture, gait impairment, mild intellectual disability, and hyperopia and astigmatism. Curiously, she is macrocephalic. Brain MRI was normal. No relevant family history or parental consanguinity are known. Prior genetic investigation did not find any pathogenic variants, but recently performed trio exome sequencing identified a de novo splicing ZC4H2 variant, not previously described. X-inactivation studies were not conducted. We hope this case helps to expand the known ZARD phenotype and to improve clinicians' recognition of this disease.







11h12 - NEW SYNDROME CAUSED BY DOMINANT VARIANTS IN MAP3K20

Presenting author: Dídac CASAS-ALBA

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MAP3K20 is a member of the mitogen-activated protein triple kinase (MAPKKK) family implicated in signal transduction. Recessive variants in MAP3K20 have been linked to two phenotypes: split-foot malformation with mesoaxial polydactyly (MIM#616890) and centronuclear myopathy 6 with fiber-type disproportion (MIM#617760). More recently, dominant variants in MAP3K20 have been found in patients with variable features, including split-foot malformation, sensorineural hearing loss, craniosynostosis, and dysmorphic features, as reported in the ACMG Clinical Genetics Meeting (1). We report a 3-year-old female patient with coronal craniosynostosis, terminal transverse defects of the limbs (with brachydactyly, syndactyly, and camptodactyly of hands and feet), facial dysmorphic features, skin lesions, and suboptimal neurological development. She has microcephaly, brachyturricephaly, sparse hair, low anterior hairline, sparse and arched eyebrows, strabismus, hypertelorism, palpebral ptosis, short nose, anteverted nares, hypoplasia of the maxilla, and anteverted ears. The skin is thickened. She shows multiple, annular, erythematous, and infiltrative lesions at any location, with a fluctuating course. She also shows erosions on fingers and toes, dystrophic fingernails and toenails, and keratosis pilaris. Histopathologic examination showed psoriasiform epidermal hyperkeratosis with numerous necrotic keratinocytes and reactive keratinocytes. Brain MRI was normal. CGH-Array and clinical exome sequencing were performed, but no disease-causing variants were found. Trio-WES revealed a *de novo* in-frame deletion of *MAP3K20* (NM 133646.3: c.837_839delCAA;p.(Asn279del)), which has been reported in two patients (1). The concurrence of craniosynostosis, severe foot and hand abnormalities and overlapping facial dysmorphic features in the patient presented here and the previously reported patients suggests the presence of a newly described syndrome caused by dominant variants in MAP3K20.

References: Rosenfeld J, Shealy A, Eble T, et al. eP223: Dominant-acting MAP3K20 variants cause split-foot malformation and sensorineural hearing loss. Genet Med. 2022. 24 (3 Suppl.):S138-S139.







11h24 - POLYMALFORMATION SYNDROME ATTRIBUTED TO ERBB3 COMPOUND HETEROZYGOUS MUTATIONS

Presenting author: Sofia Ourani

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We report a female newborn investigated in our clinic due to multiple malformations and found to be compound heterozygous for two mutations in ERBB3 gene, related to autosomal recessive congenital contractural syndrome. The patient is the first child of nonconsanguineous parents, conceived naturally. Mother had thyroidectomy due to cancer 5 years ago and is under treatment with thyroxin. Father is reported healthy. Increased risk for Trisomy 21 with nuchal translucency in the upper normal limits (2.5mm) was found on the 12th week of pregnancy. During the 2nd trimester, ultrasound findings of bilateral club feet, polyhydramnios and possible cerebellum hypoplasia led to amniocentesis. Karyotype and CNV-aCGH were normal. Cesarean/ delivery initiation was decided on 32+6/40weeks of gestation due to the severity of polyhydramnios leading to maternal dyspnea. The baby was immediately intubated and transferred to neonatal intensive care unit. On physical examination hypertelorism, microphthalmia, low set posteriorly rotated ears, dysplastic ear lobes, microstomia, low frontal hair line, retrognathia, smooth philtrum, medial deviation of the index finger, inability to extend both arms, fixed talipes equinovarus, dysmorphic toes and cleft palate were noted. Her muscle tone gradually increased. Brain magnetic resonance at 6 weeks revealed signs of both malformative and destructive lesions including cerebellum hypoplasia, cerebellum hemispheres asymmetry, ventriculomegaly, cortical malformation, brain hemorrhage in periventricular white matter area. Several unsuccessful extubation attempts resulted in tracheostomy at 7 weeks of life. The patient died at 2 months due to respiratory failure.

Trio whole exome sequence revealed compound heterozygosity for the c.2595G>T, p. Gln865His and the c.2993A>G, p. Lys998Arg mutations in ERBB3 gene. Both are missense variants, classified as variants of unknown significance according to ACMG classification.

Lethal congenital contracture syndrome 2 is recessively inherited and caused by homozygous or compound heterozygous mutations in ERBB3 gene. We believe the phenotype of our patient is consistent with the syndrome and can be attributed to the mutations we found. On top of prenatal ultrasound surveillance which can be offered in future pregnancies, the identification of concrete molecular diagnosis enables accurate family genetic counseling and prenatal diagnostic options.







11h36 - VERBERI-BRADY SYNDROME – A CASE REPORT

Presenting author: Vera Monica Ribeiro Ferreira Silva Santos

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Introduction: Ververi-Brady Syndrome (VB) is a rare development disorder that is caused by heterozygous mutations in *QRICH1* (Glutamine-rich protein 1) gene (#MIM 617387). It was first reported in 2018 and, until now, 38 individuals were identified worldwide, and only 4 are familiar cases.

The function of *QRICH1* is largely unknown. It participates in the transcriptional control of proteostasis and therefore in the unfolded response of endoplasmatic reticulum stress. Phenotypically it is characterized by dysmorphic facial features, feeding difficulties, mild developmental delay, mild impaired intellectual disability, speech delay, and laboratory abnormalities.

It is possible that *QRICH1* has a relevant interest in paediatric cancer, which assumes an important role in its surveillance and outcome.

Case Reports: We report a clinical case of a five-years-old boy that presented with global development delay. He had a severe speech delay, behavioural problems, namely anxiety, shy and quiet personality. Clinically, he has microcephaly (-2,5SD) and facial dysmorphisms (hypertelorism, prominent nose, cup shaped ears, thin upper lip and protruding lower lip) and a remarkable cafe-au-lait spot. He had a poor overall growth, maintained feeding difficulties, poor sphincter control, and recurrent respiratory infections. He had a relevant family history. His mother has severe learning difficulties, language delay, with first word at 4 years old, and presented with some similar dysmorphic features. Elevated serum creatine kinase was found in the boy.

A whole exome sequencing was performed which identified an heterozygous variant of uncertain significance in the *QRICH1* gene - c.1430_1432del p.(Glu477del), with confirmed maternal inheritance. We are currently studying his two younger brothers.

Discussion: This child and his mother have similar phenotypic features, including development delay, poor speech, and learning disabilities. We hereby intend to present the c.1430_1432del p.(Glu477del) variant in *QRICH1*, at the moment classified as a variant of uncertain significance, for eventual discussion and assessment of its relevance in oncology.







11h48 - FIRST FAMILIAL CASE OF COFFIN-SIRIS SYNDROME TYPE 7

Presenting author: Konstantinos KOLOKOTRONIS

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To date about 10 patients with Coffin-Siris syndrome type 7 (p-OMIM 618027) have been described since the first literature report (Vasileiou et al., 2018). All reported variants were de novo variants (missense, frameshift, and splice site variants) within the PHD1/PHD2 domains of DPF2, a gene that plays a role in the epigenetic regulation of transcription through the identification of histone modifications. Typical reported symptoms are global developmental delay with intellectual disability and hypoplasia of the fifth toenail, thus fitting in the phenotypic spectrum of Coffin-Siris syndrome. Apart from the intellectual disability, most patients showed feeding difficulties in infancy, failure to thrive, short stature, hearing impairment, behavioural abnormalities, and recurrent infections, as well as congenital heart and brain malformations. Dysmorphic features, such as sparse scalp hair, down-slanting palpebral fissures, thick alae nasi, or a thick lower vermillion were also reported.

Here we report on the first familial case of Coffin-Siris syndrome type 7. The index patient presented at the age of 1 year with failure to thrive, a history of a severe postnatal CMV infection, ectodermal abnormalities (brittle nails, sparse hair) and dysmorphic features. The genetic analysis showed a likely pathogenic missense variant in the PHD region of DPF2, where the already reported pathogenic variants clustered. The family analysis showed that the mother as well as the older brother of our index patient also carried the detected DPF2 variant in heterozygous state. The mother had a history of school difficulties and showed dysmorphic features (deep set eyes, thick lower vermilion, thick alae nasi, dysplastic nails), but had no history of failure to thrive and was overall milder affected. The brother showed developmental delay with autistic features and overlapping dysmorphic features but did not have a history of major growth failure problems.

To our knowledge this is the first report of an inherited variant in DPF2, underlying the importance of considering inherited DPF2 variants during the variant filtering strategy of whole exome data. This is in line with the recent report of familial occurrence of inherited variants in ARID1B (van der Sluijs et al. 2021), the major gene for Coffin-Siris syndrome, where deleterious variants also occur most likely de novo.

12h00 - NOVEL PHENOTYPES OF PRIMARY MICROCEPHALIC PRIMORDIAL DWARFISM — CASE SERIES OF FOUR PATIENTS

Presenting author: Tinatin Tkemaladze

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Microcephalic primordial dwarfism (MPD) is a very rare disease with severe growth restriction and decreased head circumference (HC) that is evident in prenatal life and persists postnatally. Common features include characteristic facial features, skeletal involvement and intellectual disability, with significant phenotypic and genetic heterogeneity. We report four unrelated MPD patients whose clinical presentation suggests one or more novel MPD syndromes with normal intelligence being a common feature.

Patient 1 is a 13 yo boy born from non-consanguineous parents with severe intrauterine growth retardation (IUGR), failure to thrive, bilateral cryptorchidism, big fontanelle that is still not closed, high-pitched voice and distinctive facial features including prominent nose, wide nasal bridge and broad root, low-hanging columella, small and upslanted palpebral fissures and eyebrows, thin lips, misaligned teeth, 2-3 toe syndactyly and absence of sloping forehead. Current weight - 18kg, height -128cm, HC - 47cm. Otherwise, he is in good general health and has high academic performance at school. Brain MRI and genetic analysis has not been performed.

Patient 2 is a 8 yo girl, born from non-consanguineous parents with IUGR, failure to thrive, big and late closed fontanelle, high-pitched voice and distinctive facial features including small and sparse eyebrows, epicanthus, big forehead without sloping, micrognathia, full lips, prominent nose. Current weight - 13kg, heigh - 104cm, HC - 40cm. Otherwise, she is a healthy girl, attends elementary school and has age-appropriate cognitive development without any learning difficulties. Brain MRI has not been performed. WES results were negative.

Patient 3 is a 7 yo boy born from consanguineous parents with IUGR, failure to thrive, bilateral cryptorchidism, grade II scoliosis and facial features including triangular face, high forehead, cup shaped ears but no other distinctive facial features. Brain MRI shows dysgenesis of corpus callosum and Chiari I. Current weight - 11kg, height - 96cm, HC - 46cm. There are no other health-related issues; he attends school and has no signs of learning difficulties or psychomotor delay. Methylation analysis of imprinted chromosome 11 and 7 regions excluded Russel-Silver syndrome and WGS was negative.

Patient 4 is a 4 yo girl, born from non-consanguineous parents with IUGR, failure to thrive distinctive facial features including triangular face, frontal bossing, small mouth, thin lips, micrognathia, malar hypoplasia, low-set ears, downslanting palpebral fissures, straight eyebrows – resembling Lenz-Majewski syndrome-like face. Current weight – 9.5kg, height - 85cm, HC - 45cm. Otherwise, she is a healthy child without any other health-related issues, speaks two languages and has high academic performance at school. Karyotype showed 45,X. However, her striking dysmorphic facial features and extreme growth deficiency make us suspect existence of a dual diagnosis.

Current cases go beyond the spectrum of classical MPD phenotypes like Seckel syndrome or microcephalic osteodysplastic primordial dwarfism (MOPD) and broaden the phenotypic







spectrum of this extremely rare condition. Normal cognitive profile is a new and unusual finding for primary MPD that calls for further research to understand the underlying genetic etiology especially in the context of negative WES or WGS, considering dual diagnosis in some cases as well.







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