ABSTRACT BOOK

EURODYSMORPHO 2025

35th EUROPEAN MEETING ON DYSMORPHOLOGY

September 17-20 2025, Vilnius University

Sunrise, 1904 - Mikalojus Konstantinas Ciurlionis

Wednesday 17th of September

Session 1 Warming up session

15:15: GENOME SEQUENCING FOR THE DIAGNOSIS OF INTELLECTUAL DISABILITY AS A PARADIGM FOR RARE DISEASES IN THE FRENCH HEALTHCARE SETTING: THE PROSPECTIVE DEFIDIAG STUDY

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Background Intellectual disability (ID) is the first cause of referral to medical genetic departments in French academic hospitals and is characterized by a very high level of genetic heterogeneity. Whole Genome Sequencing (WGS) as a first diagnostic approach has been shown successful in other countries and is expected to achieve a higher diagnostic yield than the French national reference strategies (RefSrategy) (fragile X expansion testing, chromosomal microarray analysis and 44 ID genes panel), given its breath and more homogeneous coverage, its ability to identify copy number, structural and intergenic/deep intronic events.

Methods DEFIDIAG is a national multidisciplinary, prospective, diagnostic pilot study carried out in the framework of the French initiative for genomic medicine (*Plan France Médecine Génomique 2025*) aimed at comparing the diagnostic yield of genome sequencing *trio* analysis (WGS-trio) (index case, father, mother) with the RefSrategy in real-life conditions of clinical and laboratory workflows. Both strategies were applied in a blinded fashion in a population of 1239 ID probands (50% was previously investigated) with no definitive clinical diagnosis. Among them, a subgroup of 187 patients were randomized to undergo WGS *solo* (proband only) in addition to WGS-trio and RefSrategy.

Results 442 likely pathogenic/pathogenic single nucleotide variants (SNVs) were identified (for 231 genes) as well as 171 variants of uncertain significance warranting clinical or functional reassessment for a potential reclassification (VUS+) (for 142 genes), 79 likely pathogenic/pathogenic Copy Number Variants and 10 likely pathogenic/pathogenic Structural Variants. The diagnostic yield for likely pathogenic/pathogenic variants increased from 17.3% with the RefSrategy to 41.9% with WGS-trio in the never explored patients cohort. An increase of 13.9% was observed in all categories by adding the VUS+, thus raising the potential yield to 56% for WGS-trio. Overall, WGS *solo* enabled the identification of likely pathogenic/pathogenic variants in 29.9% of cases (increasing to 41.1% when including VUS+) compared to 21.9% with the RefSrategy. In addition, following recent reports of *de novo* variants in the non-coding spliceosomal *RNU4-2* gene as a common cause of ID, this gene was

subsequently analyzed that made it possible to identify a recurrent pathogenic *de novo* variant in 7 patients.

Conclusions As a first line test for ID diagnosis, WGS (including on *solo* situations) has proven to be more effective than the reference strategies, in the context of real-life hospital setting in France.

15:30: A NEW MULTISYSTEM DISORDER, TIMES SYNDROME, REVEALS UNEXPECTED ROLES OF VOLUME-REGULATED ANION CHANNELS

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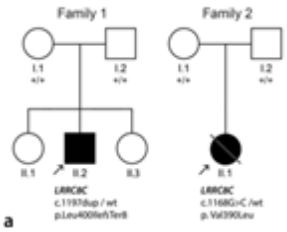
We describe two individuals with a congenital disorder including Teleangiectasia, Intellectual disability, Microcephaly, Metaphyseal bone dysplasia, Eye anomalies and Short stature (TIMES syndrome) and a specific facial appearance (Fig. 2,3,4). The unrelated patients had different never-seen *de novo* variants (a missense and a fs/stop) in a region of the *LRRC8C* gene, encoding the boundary between the pore and a cytoplasmic domain, that is depleted of sequence variations in control subjects (Fig.1).
The LRRC8C gene codes for a subunit of Volume-Responsive Anion Channels (VRACs) channels of the cell membrane that are activated by external hypotonic conditions and allow the cell to discharge water and solubles and protect itself from osmotic swelling. Although molecular structure and functioning of VRACs are well known, their specific physiologic roles in the body have remained elusive.
We found that LRRC8C proteins with the patients' variants were incorporated into mature VRACs but the VRACs showed destabilization of subunit interaction and, importantly, enhanced activation, resulting in channel activity even at isotonic conditions in which wild-type channels are closed (Fig 5,6,7). The pathogenetic chain between constitutive VRAC activation and the pleiotropic clinical phenotype is still unclear at present; potentially affected cell types are endothelial cells, neurons in the developing brain, growth-plate chondrocytes, and others.
Thus, the TIMES syndrome is a pleiotropic, clinically recognizable condition produced by monoallelic dominant LRRC8C variants leading to constitutional activation and gain-of-function of VRAC channels. It highlights first links between VRAC function and health and disease and might be amenable to pharmacologic treatment in the future.

Fig.1



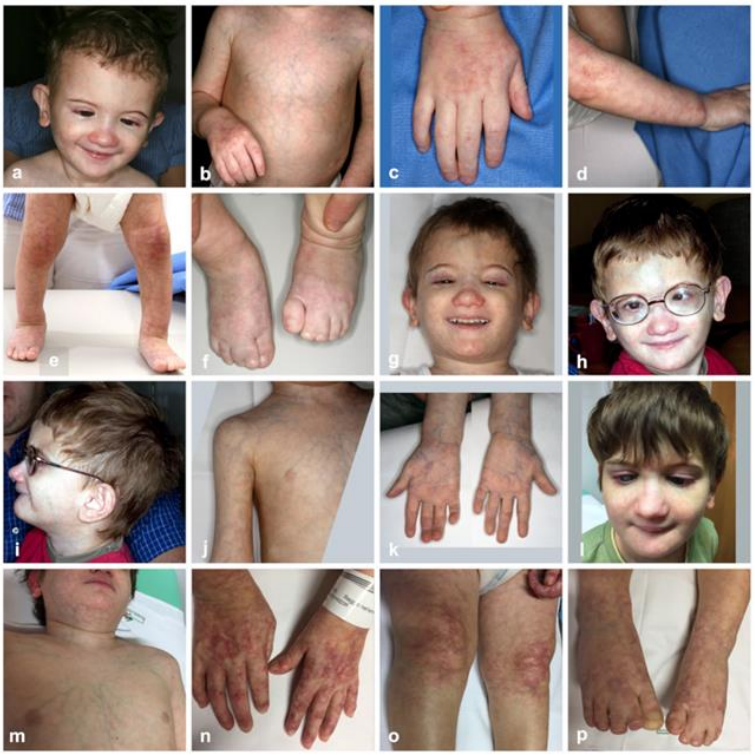


Fig. 2 Patient 1 a,g-i,l Dysmorphic features at different ages: small face, epicanthal folds, entropion and bulbous nasal tip. He also had a marked cutis marmorata. that is still persisting at the age of 17 years (b-f, j-k, m-p). In addition, he had genua vara (e), slightly short thumb (c,k,n), II-III and IV-V toe syndactyly on the right side and II-III toe syndactyly on the left side (f,p). At 2 years and 7 months, his length was 77.5cm (<1st percentile, -4.0 SD), his weight was 7740g (<1st percentile, -4.5 SD), his head circumference 42cm (<1stpercentile, -4.6 SD) and pubertal stage A0 P1 S1 with 1ml testes bilaterally in the inguinal canal. At 12 years 2 months, his height was 112cm (<1st percentile, -5.1 SD), his weight 27kg (<1st percentile, -6.5 SD) and his head circumference 48.5cm (<1st percentile, -3.6 SD). The pubertal stages were A0 P1 B1 with 1ml testes bilaterally in the inguinal canal.

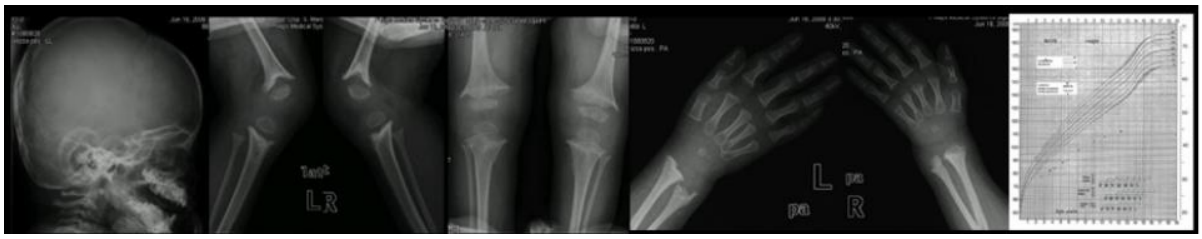


Fig. 3 Patient 1 X-Rays of the skull**:** large bregmatic fontanellae ; thin frontal and parietal skull; wormian bones X-Rays of lower limbs: **C**up flaring of the distal femur metaphysis and of the proximal tibial and fibular metaphysis with irregular ends; thin cortical diaphysis; X-Rays of the hands: cup flaring of the distal radius and ulna, flaring of the distal 2nd, 3rd, 4th metacarpals and of the proximal phalanx of the 2nd, 3rd, 4th finger Bone age: 9 months (Greulich e Pyle) (age 2 years 3/12)

Fig. 4 Patient 2 She had microcephaly, deep set eyes, a short and upturned nose, marked cutis marmorata telangiectatica congenita, global developmental delay (she was non-verbal), intellectual

disability and spastic cerebral palsy. She had seizures with onset at 4 months of age. Skeletal X-rays had demonstrated gracile long bones, poorly developed glenoid fossa, slender ribs and overtubulated long bones with mild metaphyseal irregularities. At age 15 she developed acute idiopathic hypertension, with systolic blood pressure exceeding 200. She presented in acute respiratory failure and developed gastric necrosis that was not amenable to surgery. She died three days after admission

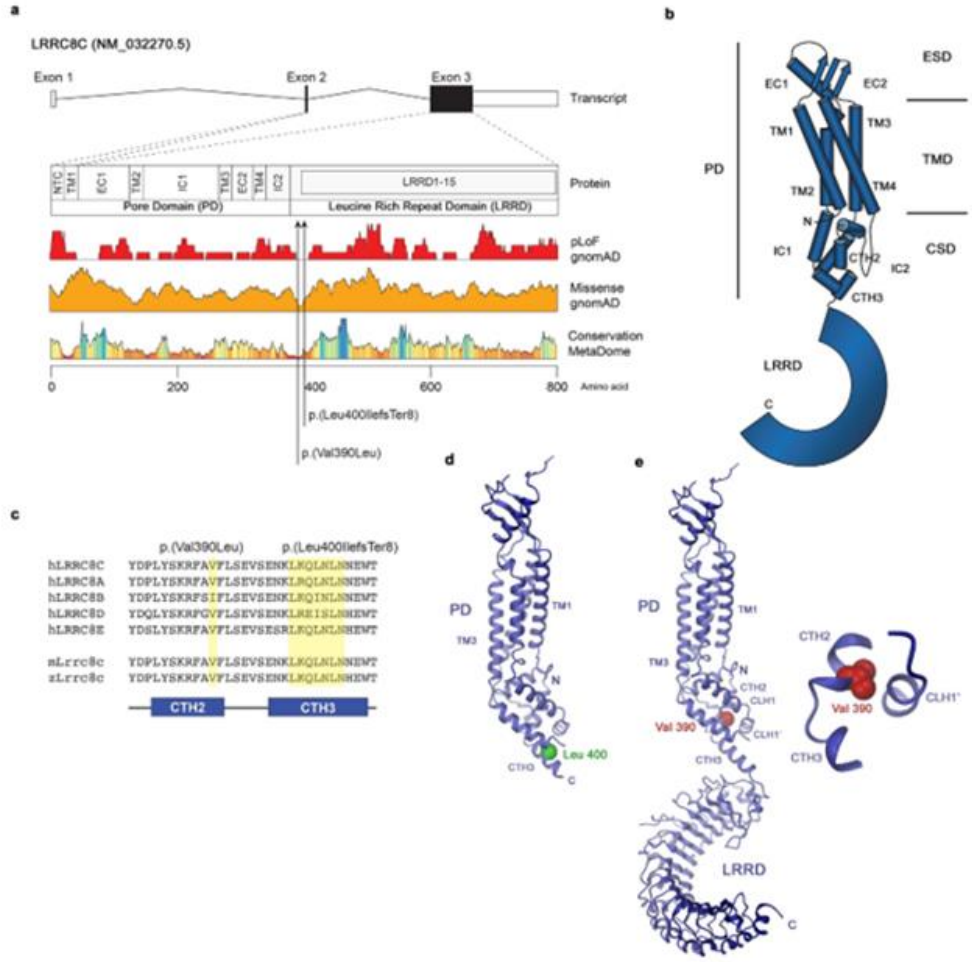


Fig 5 Characteristics of LRRC8C and of the variants identified. (A) Schematic representation of the main LRRC8C transcript and its protein product. Both LRRC8Ctrunc (p.Leu400IlefssTer8) and LRRC8CV390L (p.Val390Leu), depicted by black arrowheads, fall into a region of the protein that is bereft of loss-of-function (pLoF, red track) or missense (orange track) variants in normal controls, as reported in the gnomAD database of normal controls, likely representing a sensitive site for DNA changes to result in pathogenic variants, as also shown by the MetaDome track (red, highest intolerance to changes; blue, lowest intolerance to changes). NTC N-terminal coil, TM transmembrane domain, EC extracellular loop, IC intracellular loop, LRRD leucine-rich repeat domain. (**B) LRRC8C topology with secondary structure element of the pore PD indicated and the LRRD approximated as blue arc.** (**C) Conservation of the CTH2 and CTH3 region domains**, with respect to the amino acid residues impacted by LRRC8Ctrunc and LRRC8CV390L, in human paralogues of LRRC8C (hLRRC8x) and orthologues from mouse (mLrrc8c) and zebrafish (zLrrc8c). LRRC8C is not present outside of bony vertebrates. **(D) Model of the protein construct LRRC8Ctrunc based on the murine LRRC8CWT structure (PDBID: 8B40).** The position of Leu 400 is indicated as a green sphere. (**E) Structure of the murine LRRC8CWT subunit with the position of Val 390 indicated as red sphere.** Inset (right) shows blowup of the region around Val 390 with its side chain represented as CPK model.

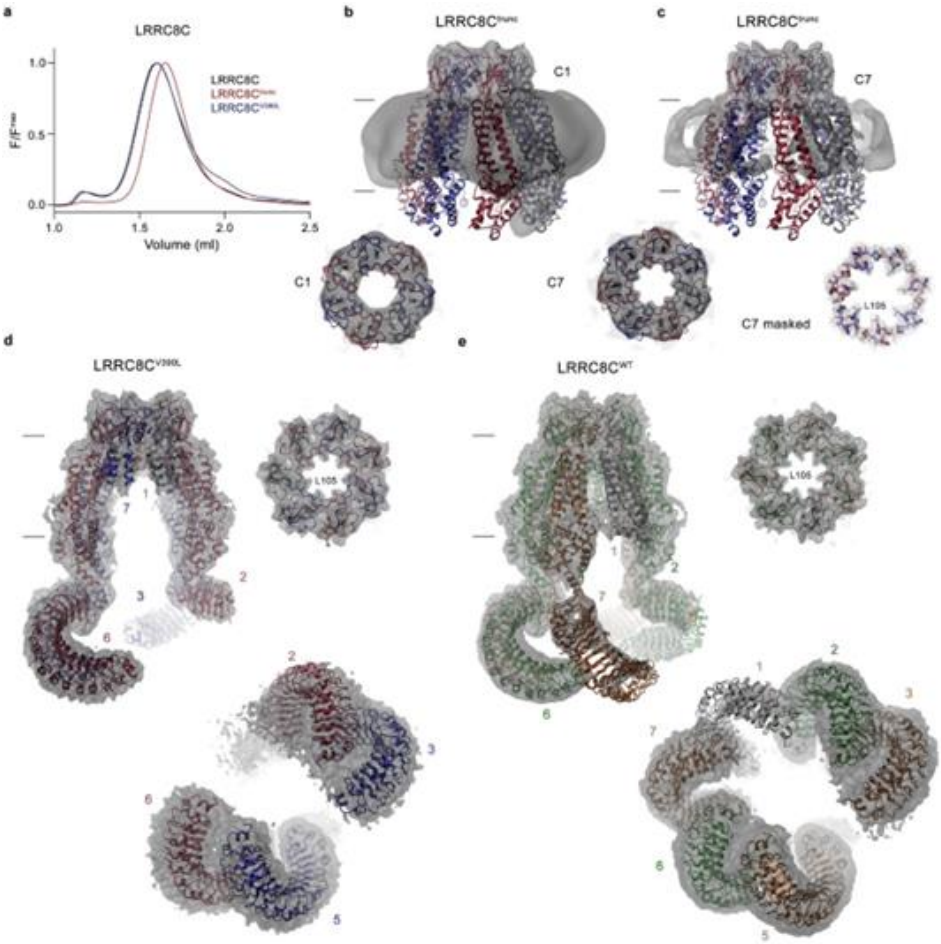


Fig.6 Structural properties of LRRC8C disease mutants

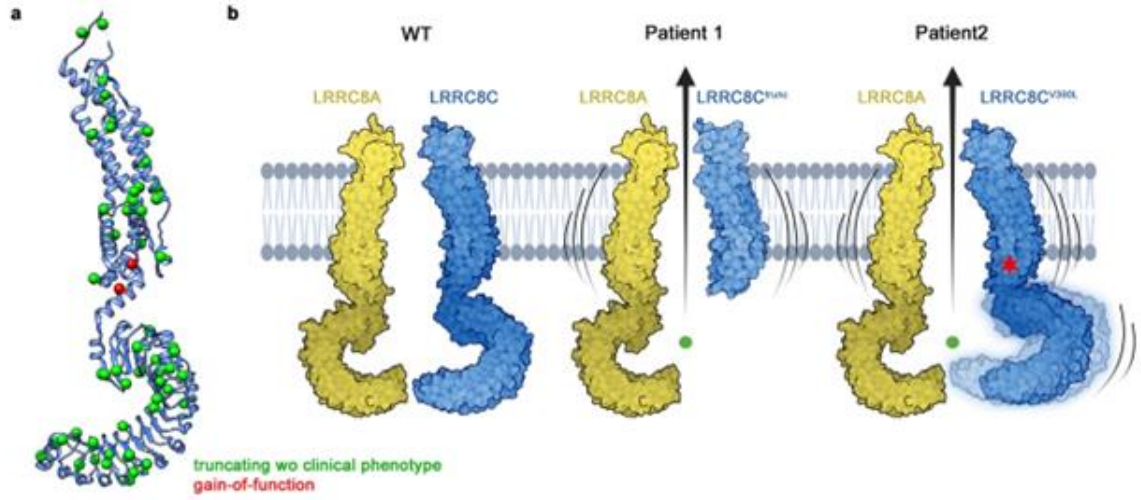


Fig 7 Phenotype of human LRRC8C variants

15:45: FINDING THE RIGHT VARIANT(S) - THE FIRST ANSWER ISN´T ALWAYS THE BEST NOR THE ONLY ONE: A SMALL VIVID CASE SERIES

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Introduction: In times of whole genome sequencing and the ongoing progress in identifying new gene-disease associations, we are confronted daily with an abundance of information. Especially in patients with complex medical conditions, we often encounter multiple suspicious variants in disease-associated genes during diagnostics. Determining their clinical relevance and role in the patients' symptoms can be quite challenging.

Methods: We present four examples from our clinical practice whose diagnostic journeys illustrate the challenges we encounter along the way.

Results: *Patient 1*, A 2-year-old boy with epileptic encephalopathy associated with West syndrome and an initial finding of a heterozygous variant of uncertain significance in the *GRIN2A* gene. Additional symptoms include postaxial polydactyly and characteristic facial features. -> Reclassification of the variant of uncertain significance in *GRIN2A* as likely benign and detection of a heterozygous deletion of exons 1 and 2 of *ANKRD11*.
Diagnosis: **KBG syndrome (MIM 148050)**

Patient 2, A 2-year-old girl with primary microcephaly (- 6,3 z), transient postnatal hypoglycemia, and macroglossia. ->Detection of a de novo heterozygous likely pathogenic variant in *KIF11* and mosaic IC2 hypomethylation. Diagnosis: *KIF11*-associated microcephaly with or without chorioretinopathy, lymphedema, or impaired intellectual development; **MCLMR (MIM 152950) and Beckwith-Wiedemann syndrome (MIM 130650).**

Patient 3, A 14-year-old boy with combined developmental disability, short stature, scoliosis, distinctive facial features, and distal limb anomalies. -> Detection of a heterozygous *de novo* likely pathogenic variant in *TAOK1* and a *de novo* variant of uncertain significance in *BPTF1*. Diagnosis: *TAOK1*-associated developmental delay with or without intellectual impairment or behavioral abnormalities; **DDIB (MIM 619575) and suspected** *BPTF*-associated neurodevelopmental disorder with dysmorphic facies and distal limb anomalies; **NEDDFL (MIM 617755**).

Patient 4, A 1-year-old boy with primary microcephaly (- 4,9 z), muscular hypertonia, minor facial anomalies, and initial finding of a heterozygous likely pathogenic variant in *NARS1* -> Identification of the Variant *NARS1* as maternally inherited and classification as carrier status for *NARS1*-associated autosomal-recessive disorder (MIM 619091). Trio genome sequencing revealed a heterozygous *de novo* likely pathogenic variant in *CHD3*. Diagnosis: **Snijders-Blok-Campeau syndrome (MIM 618205)**.

Conclusion: A discrepancy between the symptoms described in the literature and the individual clinical presentation may be a manifestation of a variable -yet unknown- phenotype spectrum. However, it should prompt one to question whether the identified variant is truly the correct or sole cause.

16:00 THE PSYCHOSOCIAL COPING OF FAMILIES WITH CHILDREN AFFECTED BY RARE DISEASES: THE NEED FOR SYSTEMATIC AND INTEGRATED SUPPORT FROM THE MOMENT OF DIAGNOSIS

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Rare diseases (RDs) deeply affect the well-being of the entire family, causing feelings of guilt and emotional burden for parents (Baumbusch et al., 2019). Reaching a diagnosis for a rare disease can take years, during which families often consult multiple specialists. Even after receiving a diagnosis, families often feel alone and without the necessary support structures. Children and young people with RDs experience social exclusion and low self-esteem, especially during adolescence (Somanadhan et al., 2023). Parent caregivers suffer from chronic stress and are required to take on multiple roles, including coordinating treatment (Černe et al., 2024). Psychological support is often inadequate, even though it is essential for family coping (Witt et al., 2023).

A study conducted in Estonia, as part of a broader research initiative, has an aim to identify burdens of carers of people living with RDs. The ongoing study uses a questionnaire developed in Australia (Anderson et al., 2013), which has been adapted to the Estonian context. We have currently 72 responses.

To receive a correct diagnosis, 33% of patients and their carers had to visit one to two medical doctors, while 39% had to consult with three to five other medical specialists. The final diagnosis was most commonly made by a medical geneticist (69%). After receiving a diagnosis, 28% of respondents were offered psychological support. This was most often recommended by a medical geneticist (47%), while in 11% of cases, a family member or close person encouraged them to seek support. Overall, 59% of respondents were satisfied with their diagnosis, but a significant proportion (18%) expressed dissatisfaction.

Only 30% of respondents had found an organization or support group in Estonia for people with a similar diagnosis. At the time of diagnosis, only 16% were informed about the existence of support groups, while 65% received no information. 95% of respondents agreed that patients should be offered information about support groups and organizations upon confirmation of the diagnosis. 46% of respondents had been in contact with other families or patients with the same or a similar disease. The study results show that 38% of respondents felt they had been given sufficient information about their disease. Only 23% had the opportunity to participate in training sessions and workshops.

In the past year, patients most frequently visited a family doctor (31% of respondents). Neurologist visits were also common (15%). In addition to doctor visits, contact with healthcare support services was crucial. Over the year, patients had a total of 575 physiotherapist and 226 occupational therapist visits. Speech therapy services were used by 10% of respondents, with a total of 329 visits. Psychological services were also significant—10% of respondents used them, with a total of 117 sessions.

Our results indicate to a clear need to improve awareness and provide consistent, systematic emotional support from the point of diagnosis. The healthcare system must offer integrated and multidisciplinary support that includes medical treatment, psychological counselling, social services, and active family involvement. Only such a holistic approach can improve the quality of life for children with RDs and their families and reduce feelings of isolation and overload.

Funding: PRG2040

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16:15 HAND ABNORMALITIES IN YUNIS-VARON SYNDROME: A SYSTEMATIC REVIEW

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Yunis-Varon syndrome (YVS) is an autosomal-recessive disorder caused by pathogenic variants in the FIG4 gene. It presents with multiple congenital anomalies including cleidocranial dysplasia, digital hypoplasia, and severe neurological involvement.

We present here a case report and systematic review of all 32 previously published cases. 12 cases, including the case reported here, were confirmed to have biallelic variants in FIG4, with the remaining 21 cases being reported prior to the identification of the causative gene.

11 of the 12 cases (92%) with biallelic FIG4 variants exhibited a symmetrical pattern in which the first digit of the hands and feet was more severely hypoplastic than the other digits with absent nails. Milder distal hypoplasia or aphalangia was typically present in the remaining digits. In seven cases (58%) the second digit was less severely affected than the first digit, but more severely affected than the remaining digits, giving a '1, 2, =(3-5)' pattern.

Previous case reports were reviewed for this pattern of digital hypoplasia. Of the 21 cases not found to have FIG4 variants, 13 exhibited the same symmetrical pattern of digital hypoplasia, and other features consistent with YVS syndrome were common, including early demise.

The eight cases (24%) which did not fit the digital hypoplasia pattern, which included three cases in which Sanger sequencing did not detect FIG4 variants, lacked many other features consistent with YVS, and exhibited a broad range of age at demise or last follow-up, including two adults. These cases most likely represent misdiagnoses.
The prognosis in YVS is poor but variable. When excluding cases likely to be misdiagnoses, the median age of demise or last follow-up is three months, with the eldest live case being 14 years of age.

Session 2 Syndrome delineation

17:00 RECURRENCE OF FETAL BRAIN MALFORMATIONS: INVESTIGATING THE ROLE OF A FAMILIAL TUBB3 VARIANT OF UNCERTAIN SIGNIFICANCE

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Tubulinopathies are a group of autosomal dominant disorders characterized by a wide spectrum of brain malformations such as lissencephaly, dysgyria and dysmorphic basal ganglia. Some signs, such as

asymmetric ventriculomegaly and hypoplastic corpus callosum, can be observed in the setting of prenatal diagnosis. The clinical presentation is variable, with most individuals presenting with neurodevelopmental delay and epilepsy, although cases with milder brain malformations and normal intellect have been described.
We report the case of a healthy nonconsanguineous couple who experienced two consecutive pregnancies whose fetuses presented with similar cerebral dysmorphisms at prenatal ultrasound. In both cases, the couple decided to terminate the pregnancy due to the clinical presentation.
The first pregnancy came to the attention of our Clinic at 20 weeks and 3 days of gestation, due to fetal brain anomalies (corpus callosum hypoplasia, ventricular asymmetry, and a slight leftward deviation of the cerebral midline). Fetal brain MRI confirmed the neurosonographic findings, showing also a possible brainstem dysmorphism, suggestive of a tubulinopathy.
Amniocentesis was performed for chromosomal microarray (CMA) and exome sequencing (ES). CMA identified a maternally inherited 745 kb deletion at 22q11.21, considered to be unrelated to the unrelated to the clinical presentation. ES detected a paternally inherited variant of uncertain significance (VUS) of the *TUBB3* (NM_006086.4) gene (c.137G>A; p.(Arg46Gln), ACMG criteria PM1 supporting, PM2 supporting, PP3 supporting), which was also present in the paternal grandmother. Noticeably, the father also showed some mild dysmorphic aspects at brain MRI, such as mild asymmetry of the ventricular system and cysts of the cavum veli interpositi, but no clinical signs.
In a subsequent pregnancy, fetal ultrasound and MRI showed again a deviation of the midline, dysmorphic ventricles and a slightly shortened corpus callosum. CMA from amniocytes was normal, while ES is ongoing. Segregation analysis confirmed the presence of the same *TUBB3* variant as in the previous pregnancy.
TUBB3 pathogenic variants are associated with cortical dysplasia complex with other brain malformations (OMIM #614039) and are often found *de novo*. To further investigate the clinical significance of the variant found in this family, a MRI has been scheduled for the paternal grandmother. We are open to discussion relative to the possible role of this variant in the fetal and post-natal phenotype: might it be causative of a milder phenotype without associated neurodevelopmental concerns?

17:15 ANTENATAL DIAGNOSIS OF SMITH-KINGSMORE SYNDROME IN A FETUS WITH SIGNIFICANT MACROCEPHALY, BRAIN AND CARDIAC ANOMALIES

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Smith-Kingsmore syndrome (SKS) is a rare neurodevelopmental genetic disorder caused by mutations in the *MTOR* gene, which plays a key role in cell growth and regulation. SKS is characterized by macrocephaly/megalencephaly, developmental delay, intellectual disability, hypotonia, and seizures. To date, around 70 individuals had been reported worldwide, and, to our knowledge, this is the second genetically confirmed antenatal *de novo* SKS case, further delineating antenatal presentations of this syndrome.

An unrelated Indian family presented with their second pregnancy. Both parents, as well as the older sibling, were healthy. The extended family history was unremarkable. Foetal anomaly ultrasound scan (USS) at 20/40 week showed a large head and brain, hypertelorism, flat midface with frontal bossing, enlarged heart with ventricular septal defect. Foetal MRI scan at 21+2/40 showed a relatively large head with cerebral hemispheres not normally formed (ill-defined neuronal migration pattern), enlarged posterior fossa of the brain with underdevelopment of the vermis cerebelli, as well as hypertelorism. Following USS showed oligohydramnios from 26/40, progressing to anhydramnios closer to the delivery date.

Due to above abnormalities, the family was seen in the Genetics Clinic at 29/40. Trio rapid Whole Exome Sequencing showed a *de novo* likely pathogenic *MTOR* c.6050C>T (p.Ile2017Thr) variant in the foetus, confirming Smith-Kingsmore syndrome diagnosis.

The baby was born at 36/40 via Cesarean section due to breech presentation. The baby required respiratory support, including intubation, and admission to NICU. The chest XR showed pulmonary hypoplasia with bell shaped appearance of thorax, and a large globular heart (confirmed on ECHO). The baby also developed bilateral pneumothoraces. The baby sadly passed away at 40 hours of life in context of a severe persistent pulmonary hypertension of newborn secondary to pulmonary hypoplasia.

17:30 NEWBORN WITH MICROCEPHALY, HYPOPLASTIC BRAIN HEMISPHERES AND CEREBELLAR ATROPHY CAUSED BY A NOVEL VARIANT IN CRNKL1 GENE

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The spliceosome is a ribonucleoprotein complex composed of 5 small nuclear RNAs and more than 50 proteins. *CRNKL1* (crooked neck pre-mRNA splicing factor-like 1), a component of the spliceosome, is a widely expressed pre-mRNA splicing factor (OMIM * 610952) (Chung et al., 2002). The CRNKL1 protein joins independently and plays roles in binding and unbinding various proteins and members of the intron-binding complex rearrange into their final positions (Haselbach et al., 2018).We currently are describing a newborn with severe microcephaly and brain anomalies caused by a novel variant in *CRNKL1* gene.
The index case is first child in the family, Slavic origin, who was born from normal pregnancy at term with birth weight 2950g (-1.0 SD), length 49 cm (-0.5 SD), and microcephaly - OFC 27 cm (-6 SD). Apgar score were 6/7/7. He presented low and sloping forehead, cutis verticis gyrata, broad nasal bridge, large ears, long fingers, bilateral simian crease, and partial T2-3 syndactyly. He had no eye contact. Increased liver was detected in ultrasound. Biochemical investigations showed very low cholesterol level (1.1 mmol/L). Cerebral computed tomography at the first day of life shows hypoplastic cerebral hemispheres with a low formation of gyri according to the gestational age (oligogyria), wide extracerebral cerebrospinal fluid spaces, absent corpus callosum, hypoplastic cerebrellar hemispheres and missing vermis. He deceased during first months of life in institution. Single exome sequencing was performed some years later in research setting, which identified rare missense c.800G>A (p.Arg267His) variant in *CRNKL1* gene. This variant was confirmed by Sanger sequencing. Parental testing was not possible.
In 2024 was on the annual ESHG meeting an oral presentation by Louise S Bicknell from New Zealand. She presented patients with severe microcephaly and pontocerebellar hypoplasia and *de novo* missense variants in *CRNKL1*, two variants that both affect the same amino acid, p.Arg267. Through exome sequencing and collaborations through Genematcher, ten individuals (including our case) has been identified with recurrent *de novo* missense variants in *CRNKL1*. All affected individuals share a common and specific phenotype: profound pre- and post-natal microcephaly, with pontocerebellar hypoplasia, seizures and severe intellectual disability. This work is accepted to AJHG (Ray Das et al 2025).
Funding: PRG2040

17:45 CLINICAL AND GENETIC INSIGHTS OF 2 CASES OF JOUBERT SYNDROME TYPE 27

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Introduction: Joubert syndrome is a rare, autosomal recessive neurodevelopmental disorder. A key feature of this syndrome is the abnormal brain development of the brain's posterior region, including the cerebellar vermis and brainstem, resulting in a characteristic “Molar tooth” sign seen on MRI scans. Physical symptoms include hypotonia, ataxia, hyperpnea, abnormal eye movements, impaired intellectual activity, dysmorphic features and seizures. Diagnosis is based on clinical, radiological and genetic testing. Over 40 genes are known to be associated with Joubert Syndrome, and *BD91* mutations are responsible for <2% of known cases of Joubert Syndrome.

Case description: First case is an 8-year-old boy, born prematurely (33hbd), developed with delay – both motor and speech delay, currently with a mild intellectual disability. Hearing test was normal The boy is under the care of a multi-specialist clinic: - Genetic Clinic - aCGH test revealed a duplication of the short arm of chromosome 16 in the 16p13.11 region of approximately 1.86 Mbp of maternal origin ; - Ophthalmology Clinic: convergent strabismus (head tilt), binocular visual defect hyperopia, nystagmus from birth, hypotrophy/hypoplasia of n II, cortical visual impairment, VEP result indicates demyelinating visual impairment ; Neurology Clinic: balance disorders, wide-based gait, slightly dilated and asymmetrical ventricular system in an MRI scan performed several years ago, EEG at the age of 4 – normal. ECHO test : no signs of heart defect or cardiomyopathy. In the last year, the mother reports accelerated growth, head circumference 56.5 cm (above the 97th percentile). In the physical examination, discrete dysmorphic features, nystagmus, widely spaced teeth, high palate, slightly widened and hollow chest, decreased muscle tone. The “molar tooth” sign, characteristic of Joubert syndrome, was identified on repeated MRI in 2025. Sequence analysis using the Blueprint Genetics (BpG) Joubert Syndrome Panel identified 2 variants of uncertain significance (VUS) in the *B9D1* gene: c.95A>G (p.Tyr32Cys) and c.1A>G (p.Met1?).
Second case is a 5-month-old boy with nystagmus noticed at birth, motor delay. Reduced muscle tension. Tendon reflexes are vivid and symmetrical. No signs of congenital defect of heart nor cardiomyopathy. Normal abdominal USS. MRI picture of brain without any abnormalities. Profile of organic acids (GCMS method) revealed phosphaturia. Sequence analysis using the Blueprint Genetics (BpG) Whole Exome identified a heterozygous splice region, intron variant B9D1 c.244+5G>A and a heterozygous missense variant B9D1 c.95A>G, p.(Tyr32Cys) – both variants of uknown significance.

Conclusion: These 2 cases contribute to the expanding clinical and genetic spectrum of Joubert syndrome. The identification of novel VUS variants in the *B9D1* gene, may contribute to the patients' phenotype, and the described symptoms, which align with core features of the disorder. However, the pathogenicity of these gene mutations remains unclear, therefore warranting further investigation. Nevertheless, their identification highlights the increasing utility of next-generation sequencing in uncovering genetic factors underlying rare neurodevelopmental disorders.

18:00 EXPANDING THE DHCR24-RELATED DISORDER’S CLINICAL AND MOLECULAR SPECTRUM THROUGH AN IN SILICO STRUCTURAL ANALYSIS APPROACH

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Desmosterolosis (OMIM 602398) is a rare autosomal recessive sterol biosynthesis disorder characterized by multiple congenital anomalies, failure to thrive, severe developmental delay, progressive epileptic encephalopathy, and elevated levels of desmosterol caused by biallelic mutations of *DHCR24* encoding 3-β-hydroxysterol Δ-24-reductase whose impairment affect the cholesterol production (1). As a result, brain cells, which rely entirely on cellular cholesterol production, are severely affected. Without adequate cholesterol, the proper formation of cell membranes is disrupted, and nerve cells are not protected by myelin, leading to cell death. The reduction in cholesterol production also has more severe effects before birth because of the rapid increase in cell number that occurs during this period (2,3). To date, 15 DHCR24 variants, from 2 related and 14 unrelated patients, have been identified in association with desmosterolosis with a variable degree of neurological impairment; of them, 11 were missense variants in homozygosity or compound heterozygosity, and 2 were nonsense variants with either 1 frameshift or 1 splicing variant in the compound heterozygous state; all were classified as pathogenic or likely pathogenic in HGMD (1). We describe a new patient harboring the novel homozygous missense variant NM_014762.4:c.506T>C, NP_055577.1:p.M169T in the DHCR24 gene. The patient came to our observation at the age of 11 years. Auxological parameters were as follows: weight: 22 Kg (<3rd centile), head circumference: 51 cm (3rd centile), and length: 123 cm (<3rd centile). At the dysmorphological evaluation, several features were noted as follows: coarse facial features, relative macrocephaly with metopic suture prominence and scapho-dolichocephalic appearance of the skull, thick eyelashes, slight bilateral epicanthus with mild downslanting palpebral fissures, bulbous nose tip, slightly anteverted nostrils with prominent columella, long philtrum with a thin upper lip, and retrognathia. At neurological evaluation, she showed severe spastic quadriplegia, multiplanar nystagmus, and bilateral exotropia. By using molecular dynamics simulation techniques, we investigated the impact of this variant on the protein stability (1). Then, we assessed its mechanistic consequences on the protein structure and functions in comparison with all known pathogenic variants, a further benign variant, and the wild-type protein. Finally, we derived distinct molecular aspects of the considered mutant proteins which were all associated with the disease manifestation giving new insights into the disorder's genotype–phenotype correlations.

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18:15 A NOVEL BIALLELIC YY1AP1 VARIANT IN SIX INDIVIDUALS WITH GRANGE SYNDROME: CLINICAL AND MOLECULAR INSIGHTS

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Background: Grange syndrome (GRNG, MIM #602531) is a rare early-onset disorder characterized by hypertension and multifocal steno-occlusive lesions involving renal, cerebral, and abdominal arteries. Additional features include bone fragility, syndactyly, brachydactyly, congenital cardiac anomalies, and intellectual disability, exhibiting variable expressivity and incomplete penetrance. Loss-of-function biallelic variants in *YY1AP1* have recently been identified as the genetic cause. To date, only 15 molecularly confirmed cases have been reported.

Methods and results: We present a detailed clinical characterization of six affected individuals (four females, two males) from the same family, with a focus on skeletal, vascular, and central nervous system (CNS) involvement. The proband (Patient 1) was referred for evaluation due to multiple fractures following minor trauma, seizures, and learning disabilities. Bone mineral density (BMD) was below -2 standard deviations (SD), and bisphosphonate therapy was initiated. Cranial MRI revealed multiple millimetric hyperintense lesions in the periventricular white matter on T2-weighted and FLAIR sequences, along with gliotic changes and volume loss in the right temporo-occipital and parieto-occipital regions (Fig. 1a). Magnetic resonance angiography (MRA) demonstrated decreased caliber of the right vertebral artery (Fig. 1b). Electroencephalography (EEG) revealed epileptic discharges, and treatment with levetiracetam was commenced. Next-generation sequencing identified a novel biallelic YY1AP1 variant (NM_001198903.1; c.2531_2532del, p.E844Gfs*), classified as likely pathogenic according to ACMG criteria (PVS1, PM2). A family history assessment identified five additional affected individuals with varying degrees of severity. In total, six patients were evaluated for skeletal, vascular, and CNS involvement. At the time of initial assessment, the mean age was 9.6 ± 4.5 years. The mean height and weight standard deviation scores (SDS) were -0.7 ± 1.1 and -0.8 ± 0.5, respectively. Five patients had a history of multiple fractures requiring medical intervention. Bone mineral density (BMD) Z-scores improved from a pre-treatment average of -4.5 ± 1.8 to -2.9 ± 1.1 following bisphosphonate therapy. Intellectual disability was present in four patients, ranging from mild to moderate severity, and seizures were observed in only one individual.

Conclusion

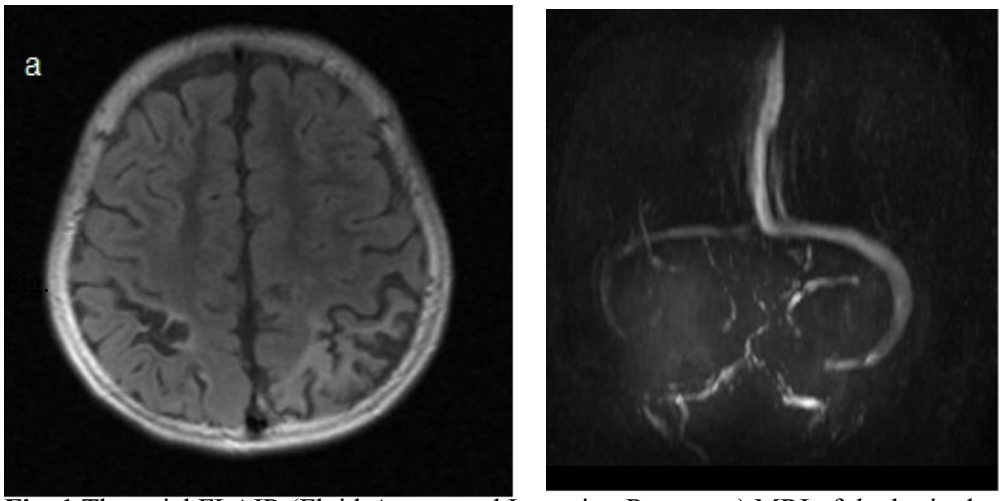

Fig. 1 The axial FLAIR (Fluid-Attenuated Inversion Recovery) MRI of the brain demonstrates volume loss in the left parietal region with associated hyperintensity, consistent with gliosis. Adjacent sulcal prominence suggests underlying tissue loss, indicative of chronic encephalomalacia (white arrows), likely secondary to prior ischemic insult (a).
This study expands the clinical and molecular spectrum of Grange syndrome by describing six additional affected individuals from a single family, highlighting phenotypic variability and multisystem involvement.
Time-of-flight MR angiography reveals decreased caliber of the right vertebral artery and hypoplasia of the right transverse sinus (b).

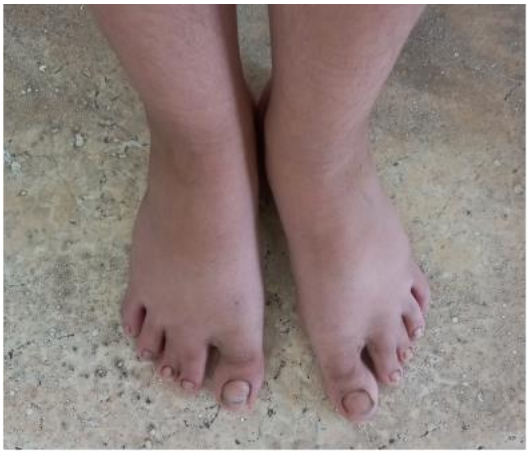

Fig. 2 Clinical photograph showing bilateral partial cutaneous syndactyly between the second and third toes.

Thursday 18th of September

SESSION 3 RNU

9:00: *Invited Talk, Zeynep Tümer, Epigenetics/DNA methylation and neurodevelopmental disorders*

9:45: GENOME SEQUENCING IDENTIFIES RENU SYNDROME IN 1% OF CASES WITHIN A GENOME SEQUNCING PROJECT

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Analysis of non-coding genomic sequences in large cohorts of unsolved individuals with neurodevelopmental disorders (NDD) led to the discovery of the ReNU syndrome, a novel genetic entity caused by de novo variants in the *RNU4-2* gene. Recent studies indicated this disorder as a frequent cause of NDD accounting for 0.4% of cases. As the *RNU4-2* gene encodes a small nuclear RNA, it is usually not included in the exome target.
In the context of the Bavarian Genome Network research project we evaluated 300 cases with unsolved NDD by applying trio short read genome sequencing (GS). The vast majority of individuals were previously examined by trio exome sequencing and for CNV analysis, however no pathogenic variant had been detected.
Overall, we identified a de novo *RNU4-2* variant within the 18 bp critical region of the gene in 3 out of 300 (1%) tested NDD individuals, thereby confirming the diagnosis of ReNU syndrome. By analyzing further in-house genomic databases we identified two more cases with ReNU syndrome. The individuals presented with moderate to severe NDD, muscular hypotonia, microcephaly and epilepsy.

Clinical examination revealed striking phenotypic similarities including a myopathic face, deep-set eyes, small alae nasi, full cheeks, an open mouth with full lips and micrognathia.
The identification of pathogenic *RNU4-2* variants in 1% of the NDD cases within the genome project confirms that this condition represents a common cause of neurodevelopmental disorders. The higher frequency compared to the published studies can be explained by the fact that the vast majority of individuals in this study were negative in exome sequencing beforehand.

10:00 THE CLINICAL PHENOTYPE OF EIGHT INDIVIDUALS WITH RNU4-2 ASSOCIATED NEURODEVELOPMENTAL DISORDER

Alma Kuechler[*1], Sabine Kaya[1], Jasmin Beygo[1], Petra Ketteler[1], Elsa Leitão[1], Kevin Lüthy[1], Harald Surowy[1], Sandra Ueberberg[1], Tobias Haack[2], Rami Abou Jamra[3], Frank J. Kaiser[1], Christel Depienne[1]

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Background/Objectives: *De novo* variants in the *RNU4-2* gene, encoding the small nuclear RNA U4, have recently been identified as a cause of a neurodevelopmental disorder (NDD), meanwhile called ReNU syndrome (OMIM #620851). Analyses of first cohorts of unsolved NDD/epilepsy patients suggested that this is a major cause.

Methods: Here, we report on the phenotype of eight individuals with ReNU syndrome from our clinical genetics department. The *RNU4-2* variants occurred *de novo* in all affected. Four individuals were identified by Sanger sequencing in a cohort of 200 exome-negative patients with moderate to severe NDD, and four were diagnosed by genome sequencing.

Results: All eight individuals show similar facial features with deep-set eyes, full lips and a large mouth, and thus a close resemblance to the facial gestalt of Pitt-Hopkins syndrome (which had previously been explicitly molecularly analyzed and excluded in some cases).
The clinical course of the eight individuals is characterized in particular by muscular hypotonia, global developmental delay, especially absence of active speech, epilepsy, and microcephaly, consistent with the phenotype of the patients published to date.

Conclusion: The identification of four in a cohort of 200 individuals, the additional four cases identified here by WGS, as well as the numerous cases published in the literature within a short period of time emphasizes that ReNU syndrome is a frequent cause that remained undiagnosed until now due to the limitations of exome diagnostics. This underlines the need for whole genome analysis to detect non-coding variants.

10:15 RNU2-2 RELATED NEURODEVELOPMENTAL DISORDER WITH BIALLELIC VARIANTS IN ACSL5 GENE: A CASE REPORT

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In April 2025 Greene et al. (DOI: 10.1038/s41588-025-02159-5) described 25 patients with intellectual disability, autistic behaviour, microcephaly, hypotonia, severe drug-resistant epilepsy and hyperventilation related to variants in *RNU2-2* gene (previously known as pseudogene *RNU2-2P*). Described patients also had common features of long palpebral fissures with slight eversion of the lateral lower lids, long eyelashes, broad nasal root, large low set ears, wide mouth and wide spaced teeth. Eleven of the described patients had n.35A>G variant.
We present a case of a now 10-year-old girl. From her first year of life she presented with delayed motor and cognitive development, hypotonia and strabismus. During the first 7-8 months she also had problems with feeding and gaining weight. When she was 1.5 years old, she was diagnosed with focal epilepsy. She has also been diagnosed with autism and attention-deficit/hyperactivity disorder. She was first sent to a medical geneticist at the age of one year, but metabolic analyses, karyotype and trio exome sequencing showed no abnormalities.
Within ongoing research project untargeted metabolome analysis and trio genome sequencing were performed. Metabolome and later lipidome analyses showed hypercholesterolemia, increased long chain fatty acid and lysolipid levels. Trio genome sequencing revealed biallelic variants in *ACSL5* gene (NM_016234.3: c.1853A>G and c.*760A>G), which has an important role in the fatty acid metabolism and may explain the lipid level abnormalities and problems with feeding and digestion. Because of no other known causes for her severe phenotype, she was put on a test diet with reduced cholesterol and saturated long fatty acids, to see if this would relieve her symptoms. After starting the diet there was a significant reduction in epilepsy episodes.
In 2025, a *de novo RNU2-2* variant n.35A>G was also found during a reanalysis of the trio genome data, which explains her intellectual disability, hypotonia, autistic behaviour and severe epilepsy. Still, since the reduced lipid diet has had a positive effect on her lipid levels and epilepsy, the diet is continued. It is unclear how *RNU2-2* and *ACSL5* variants, metabolome analysis results and patient's phenotype exactly correlate with each other. Further understanding of both *RNU2-2* and *ACSL5* genes and their phenotypic spectrum is needed.

SESSION 4 Syndrome Delineation

11:00: *Invited Talk, Outi Kuismin, Genetic Etiology of Intellectual Disability – A Finnish Perspective*

11:45: COMPARATIVE TRANSCRIPTOME OF FIBROBLASTS FROM RUBINSTEIN-TAYBI PATIENTS FOR THE IDENTIFICATION OF DISEASE BIOMARKERS

Julien Van Gils,[a,*] Slim Karkar,[b,c] Aurélien Barre,[b] Sophie Nothof,[d] Emmanauelle Taupiac,[a] Charlotte Boula de Mareuil,[a] Céline Carpentier,[e] Béatrice Cluzeau Demoures, [e] Isabelle Pellegrin, [e,f] Marlène Rio,[g] Cécile Laroche,[h] Sylvie Odent,[i] David Geneviève,[j] Ndeye-Fatou Ngom, [a] Didier Lacombe,[a] Patricia Fergelot,[a] and Frédérique Magdinier[d]

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Rubinstein-Taybi syndrome (RTS) is characterized by a typical facial dysmo r phism, distal limb abnormalities associated with intellectual disability and several additional features. Its prevalence in the general population is estimated between 1/100,000 and 1/125,000 births. Two genes are currently known to be responsible for RTS, *CREBBP* (RTS1) in 60% and *EP300* (RTS2) in approximately 8% of clinically diagnosed cases. These two paralogues code for transcriptional co-activators , respectively CPB and p300 . Both proteins contain a catalytic , Lysine Acetyl Transferase (KAT) domain involved in protein acetylation, including acetylation of histones. Therefore, RTS is regarded as a rare neurodevelopmental disorder with a significant epigenetic component. Nonetheless, due to the potential phenotypic and genetic overlap with other neurodevelopmental disorders, the development of functional assays amenable to routine clinical use represents a critical milestone for accurate patient stratification and the validation of genetic variants.

To this end, building upon our previous transcriptomic profiling of hiPSC-derived neurons from RTS patients, we conducted a transcriptomic analysis on fibroblasts to identify convergent molecular pathways and potential biomarkers suitable for diagnostic application.

Expression analysis on RTS fibroblasts identified several differentially expressed genes (DEG related to neuron differentiation and axon guidance pathways), with a majority of them being downregulated. Furthermore, our canonical correlation analysis revealed 13 DEGs identified in fibroblasts that significantly follow the same trend of 5 DEGs identified in hiPSC-derived neurons.

We showed that the dysregulation of pathways associated with neuronal differentiation and maturation in RTS cells is also detectable in patient-derived tissues that are more accessible than hiPSC-derived models, thereby offering greater potential for integration into routine diagnostic workflows. By utilizing primary fibroblasts, we identified a transcriptomic signature that may serve as candidate biomarkers indicative of reduced KAT enzymatic activity. Other type of *CREBBP* variants need to be studied but this strategy complementary to the development of DNA methylation episignatures could represent an alternative when no specific methylation profile exists or when the DNA episignature is not sensitive enough by itself to serve as a functional diagnostic tool.

12:00: VALIDATING THE CORNELIA DE LANGE INTERNATIONAL CONSENSUS STATEMENT CLINICAL SCORE IN NORTHERN IRISH PATIENT COHORT

Tabib Dabir

And suggested a scoring system Kline et al published an expert consensus document on diagnosis and management of Cornelia de Lange syndrome (dLS) in 2018. The scoring system was suggested for clinical diagnosis and indications for molecular testing of CdLS. A retrospective study of all patients in Northern Ireland (NI) who were tested for Cornelia de Lange Syndrome (CdLS) was carried out. This was carried out by requesting data from regional genetics lab on all patients who were tested for CdLS. Patients identified from 100K Genome Project and DDD Study patients were

also included. Information was obtained using clinical notes, electronic care record and patient photographs.
The main aims were; to identify the prevalence of CdLS in NI, test the validity of *Kline et al 2018* International Consensus Statement clinical score and identify any genotype – phenotype correlations in our cohort.
Total 33 patients were tested for CdLS. There were 19 confirmed cases; 10 of which were 'classical CdLS' and 9 were 'non-classical' as per the scoring system. Two further cases were classified as likely CdLS on clinical grounds. The NI prevalence was found to be lower than reported prevalence elsewhere. Gene variants identified included NIPBL (47%), SMC1 (16%), RAD21 (11%), SMC3, (16%), BRD4 (5%), HDAC8 (5%). All 'classical' cases had the listed cardinal facial features and all had NIPBL variants, except for one BRD4 case. Other variants scored in the 'non-classical' range between 4 and 10. Most common features include philtrum and lip abnormalities, intellectual disability, post-natal growth restriction.
In conclusion we believe the scoring system is robust and no suspected cases would have been missed on molecular testing using the scoring system. However it appears to be skewed towards NIPBL and other CdLS gene variants show a 'non-classical' phenotype. The scoring system may be less useful in gene agnostic era but would still be useful for phenotyping and variant interpretation.

12:15: MYHRE SYNDROME: A RARE DIAGNOSIS UNCOVERED BY EARLY GENETIC TESTING

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Myhre syndrome is a rare autosomal dominant connective tissue disorder caused by pathogenic variants in the *SMAD4* gene. It is characterized by progressive fibrosis, distinctive facial features, short stature, joint stiffness, cardiovascular abnormalities, and variable intellectual disability.
We report the case of a female patient referred to clinical genetics due to short stature, transient hyperprolactinemia, ventricular extrasystoles, and frequent infections. She was born small for gestational age (weight –2.2 SD, height –1.5 SD) and presented with syndactyly of both toes, a left-sided transverse palmar crease, and normal psychomotor development. At the time of evaluation, her anthropometric measurements were: height –1.5 SD, weight –2 SD. Karyotype was 46,XX.

Next-generation sequencing (NGS) identified two heterozygous variants:

1. A pathogenic de novo variant in *SMAD4*: c.1498A>G, p.(Ile500Val), confirming a molecular diagnosis of autosomal dominant Myhre syndrome;
2. A variant of uncertain significance (VUS) in *SMARCE1*: c.372A>G, p.(Ile124Met), inherited from her unaffected father.

Myhre syndrome is rarely diagnosed in early childhood due to its evolving and variable clinical presentation. In this case, short stature, subtle dysmorphic features, and suggestive growth and health history prompted early genetic testing. The identified *SMAD4* p.(Ile500Val) variant is the most frequently reported pathogenic variant in *Myhre syndrome* to date so far.
This case underscores the importance of early genetic evaluation in children presenting with unexplained growth delay and syndromic features. Given the progressive nature of *Myhre syndrome*, early diagnosis allows for appropriate surveillance, management of potential complications, and preventive measures regarding surgical and anesthetic risks due to underlying tissue fibrosis.

12:30: TARGETET DIAGNOSTICS OF MUSCULOCONTRACTURAL EHLERS-DANLOS SYNDROME IN TODDLER- ILUSTRATIVE CASE AND SHORT LITERATURE REVIEW

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Musculocontractural Ehlers-Danlos syndrome is a rare systemic disease characterized by congenital multiple contractures, characteristic craniofacial features (like large fontanel, hypertelorism, downslanting palpebral fissures, blue sclerae, ear deformities, high palate) evident at birth or in early infancy, and characteristic cutaneous features like skin hyperextensibility, skin fragility with atrophic scars, easy bruising, and increased palmar wrinkling. The average age of onset of the first episode of joint dislocation and subcutaneous hemorrhage is 6 years of age. Specific phenotype is not yet well understood, probably due to the ultra-rarity of the disease.
I would like to present a single case of musculocontractural Ehlers-Danlos type 1 syndrome.
Klara was born as the second child of healthy non-consanguineous parents in 38 week of pregnancy (complicated by gestational diabetes, two-vessel umbilical cord, oligohydramnios), by complicated delivery (clavicle fracture), weight 2390g, 10 Apgar points. After birth there were observed: deformation of feet (right equinovarus, right valgus), suspicion of hips dysplasia, displacement of the anus. Her development seems normal – independent sitting at 6-7 months, no walking, starts to speak first words. Comparative genomic hybridization to microarray (aCGH) - no abnormalities.

At first presentation in our out-patient clinic, at 13 months of her life, we observed transparent and loss skin (especially visible on face), soft tissues puffiness in the area of face and neck, broad and flat forehead, hypertelorism, blue sclerae, thin upper lip, ears- small, soft and rotated, microretrognatia, long fingers, adducted thumbs, long toes, right feet equinovarus, displacement of anus.

The first clue was "some" connective tissue disease according to its mild features. Face2gene showed a high probability of diagnosis of musculocontractural Ehlers-Danlos syndrome. Next generations sequencing revealed 2 new variants in *CHST14* gene (frameshift), we confirmed biallelic location of the variants (one inherited from the mother, the other from the father).

12:45: A SEVERE AND RARE PHENOTYPE OF SCN4A-ASSOCIATED CONGENITAL MYOPATHY: TWO CASES WITH EARLY LETHAL COURSE IN PATIENTS WITH BIALLELIC VARIANTS IN SCN4A

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Introduction: Pathogenic variants in the *SCN4A* gene (NM_000334.4) are primarily associated with autosomal-dominant skeletal muscle channelopathies such as myotonia. However, autosomal-recessive phenotypes with congenital myopathy have also been reported. Here, we present two

newborns with congenital arthrogryposis and severe pulmonary hypoplasia, in which biallelic variants in *SCN4A* were detected post-mortem.

Methods: prenatal and postnatal phenotyping, as well as post-mortem HPO-based trio genome sequencing.

Results: Patient 1 presented prenatally (33+0 GW) with polyhydramnios, reduced fetal movement and pulmonary hypoplasia. The child showing generalized muscular hypotonia and arthrogryposis. He died one day after birth due to hypoxic respiratory failure. Patient 1 carried a homozygous variant in SCN4A: (c.1138C>T, p.(Arg380Trp)), classified as likely pathogenic.
Patient 2 was born at 28+2 GW and presented with polyhydramnios, generalized muscular hypotonia, arthrogryposis and severe pulmonary hypoplasia and died on day 10 due to hypoxic respiratory failure. Patient 2 carried two biallelic variants of uncertain significance in SCN4A: (c.3760G>A, p.(Val1254Met) and c.4489T>C, p.(Ser1497Pro)).

Conclusion: The combination of arthrogryposis, muscular hypotonia and pulmonary hypoplasia, as well as neonatal lethality, suggests a severe form of congenital myopathy. The identified *SCN4A* variants are likely cause of this rare and lethal clinical presentation. However further experiments confirming that these *SCN4A* variants impair the channel activity are required to confirm the pathogenicity. Missense variants in the *SCN4A* gene should be considered as a potential cause in fetuses and newborns with congenital arthrogryposis.

SESSION 5 Syndrome Delineation

14:30: *Invited Talk, Ann Nordgren, Childhood cancer predisposition syndromes*

15:15: CASE REPORT OF A FAMILY WITH MACROCEPHALY AND A MAX GENE SPLICING VARIANT – POSSIBLE OVERLAP OF TWO DISTINCT PHENOTYPES

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Introduction: In the Online Mendelian Inheritance in Man® database, the *MAX* gene (MIM: *154950) has been associated with two phenotypes: Susceptibility to pheochromocytoma (MIM: #171300) and Polydactyly-macrocephaly syndrome (MIM: #620712). The latter is caused by a recurrent p.Arg60Gln variant. Pheochromocytomas have been reported as the result of loss-of-function variants with a two-hit hypothesis – the germline variant predisposes to cancer. However, the disease only develops if the second allele is lost or mutates somatically.

Case: We report the case of a 3-year-old boy with macrocephaly, delayed language development, and autistic behavior. He was born at term (39 gestational weeks) from a normal pregnancy via induced vaginal delivery as the first child in the family. His birth parameters were normal: birth weight 3640g (+0.75 SD), length 51 cm (+0.25 SD), OFC 38 cm (+2.5 SD), and Apgar scores of 9/9. Brain ultrasound showed no indication of hydrocephalus. His early motor development was normal;

independent walking was achieved at 14 months. Echocardiography at the age of 1y10m revealed a small atrial septal defect that did not require surgical intervention. His speech and language development has been delayed - he had some words at 18 months of age, which later disappeared. He has been receiving regular speech therapy, and his mother reports some improvement. He has difficulties adjusting to new situations, maintaining eye contact, and expressing himself. It remains to be ascertained how much of these issues are due to the difficult home situation where the parents are separated. Clinical psychologist and ophthalmologist evaluations have been unsuccessful due to the patient's lack of cooperation.
He was referred to a clinical geneticist due to the developmental delay at the age of 3 years and 2 months. Objectively, he has a slightly dysmorphic phenotype with a prominent forehead, down-slanting palpebral fissures, short philtrum, and open mouth. Weight 16 kg (+0.6 SD); height 100 cm (+0.5); OFC 55,7 cm (+3.3 SD). The family history is complicated. Interestingly, the mother also has an OFC of 58.5 cm (+3 SD), and the grandmother has a history of pheochromocytoma.
Gene panel analysis for developmental disorders and inborn errors of metabolism was requested. Next-generation sequencing was performed using the Exome 2.5 Enrichment kit (Illumina) and NovaSeq X Plus (Illumina) platform. A rare splicing variant in the MAX gene was reported: NM_002382.5(MAX):c.172-2A>G p.?. The same variant has one ClinVar submission as pathogenic for hereditary cancer-predisposing syndrome (pheochromocytoma). Heterozygous *de novo* variants in the same gene, mainly the recurrent p.Arg60Gln variant, have been reported as a cause of the macrocephaly-polydactyly syndrome.

Discussion and conclusion: We found it interesting that, in our case, the cancer-predisposing variant was found in two patients who also displayed macrocephaly. We believe this variant could contribute to the phenotype. However, further tests are necessary to understand the extent. We have collected skin fibroblast cultures from the patient and his mother to perform RNA sequencing analysis and better understand the functional impact. We are planning to do a segregation analysis involving the grandmother with pheochromocytoma and an X-ray analysis of the hands and feet of the patient and his mother.

Funding: PRG471, PRG2040

15:30: EXPERIENCE IN UNDIAGNOSED HACKATON: PATIENT WITH PIP5K1C GENE VARIANT THAT CAUSE NEURODEVELOPMENTAL DISORDER

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Background: Whole exome sequencing (WES) is state of the art method in neurodevelopmental disorders genetic diagnostics. Unfortunately, WES diagnostic yield is only 40% and more then a half patients remain undiagnosed. One of the option is enroll patient to Undiagnosed hackathon, that is an event in which participants engage in intensive, collaborative problem-solving over a short period. We report successful diagnosed case of ultra rare genetic cause of the neurodevelopmental disorder.

Case report: our patient is 6 years old male from the first uneventful pregnancy of healthy Lithuanian couple. He was born at 37th week of gestation. In the first month of life the patient diagnosed with microphthalmia, ventricular septal defect, chordee. 2 weeks of age the pyloric stenosis was diagnosed, and he had surgery for that. Patient suffered from atopic dermatitis and food allergies. Severe developmental delay and irritability were noticed from infancy. At 1 year of age the patient had his first

epileptic seizure and in the course of the disorder he diagnosed treatment resistant epilepsy. Brain MRI showed temporal lobe hypoplasia, hypoplastic corpus callosum, arachnoid cyst and ventricular asymmetry. The patient had recurrent apnea episodes due to small jaw and tongue position.
He also had facial dysmorphism: microcephaly and plagiocephaly, high arched eyebrows, short palpebral fissures, hyperthelorism, short nose, micrognathia, dysplastic low set earlobes.

Genetic testing: The patient had extensive genetic testing that was available in Lithuania. SNP-array performed during the first years of life – no significant findings. Whole Exome Sequencing (WES) in 2022 and reanalysis of WES in January 2024 – no pathogenic variants identified. At the time of the WES and its reanalysis, trio-based analysis was not feasible. Additionally, the *PIP5K1C* gene was, at that point, only associated with an autosomal recessive disease and therefore was not prioritized for further investigation.
In 2024, the patient was enrolled in the Undiagnosed Hackathon, which enabled access to advanced genomic technologies. Following the WES reanalysis, a decision was made to perform long-read trio genome sequencing (PacBio) and optical genome mapping (Bionano). These analyses confirmed a recurrent de novo missense variant in the PIP5K1C gene: NM_012398.3(PIP5K1C):c.662A>G, p.(Tyr221Cys).

Discussion: Phosphoinositides (PIs) are membrane phospholipids produced through the local activity of PI kinases and phosphatases that selectively add or remove phosphate groups from the inositol head group. PIs control membrane composition and play key roles in many cellular processes including actin dynamics, endosomal trafficking, autophagy, and nuclear functions. *PIP5K1C* gene encodes an isoform of the phosphatidylinositol 4-phosphate 5-kinase (PIP5KIγ). De novo missense variants are related with neurodevelopmental disorder with specific dysmorhic features and epilepsy. Only 9 children is reported in the literature to date.
Conclusions: it is important collective effort in undiagnosed complex cases. It is also important to implement various sequencing techniques for this group of patients to aid a diagnosis.

15:45: FAMILIAL CASE OF TRUNCATING VARIANT IN SRCAP GENE OUTSIDE FLOATING - HARBOR SYNDROME LOCUS: A DISTINCTIVE PHENOTYPE

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Background: *SRCAP* gene encodes ATPase, which participates in incorporating histone variant *H2A.Z* in nucleosomes. Variants that appear in 33 and 34 exons of *SRCAP* gene cause Floating Harbor syndrome. However, truncated variants occurring outside mentioned exons, cause developmental delay, hypotonia, musculoskeletal defects, and behavioral abnormalities (*DEHMBA*) (OMIM #619595).

Case report. We report two male siblings,who received medical attention for different reasons. First one, 42 years old, diagnosed with atypical hemolytic uremic syndrome and is seen in the Nephrology department. He also has epilepsy since childhood, that presents with frequent seizures, worsening memory. Brain MRI showed no pathologic changes. He was referred to clinical geneticist, who noticed asthenic constitution, elongated face and slender upper extremities.
Second sibling, 36 years old, was referred to clinical geneticist for the suspected Marfan syndrome. Patient has congenital dysplasia of mitral and aortic valves and underwent surgery during adolescence. He is followed up by cardiologist for the aortic dilatation. Clinical geneticist noticed quite similar

phenotype as his brother's but also crowded teeth was noticed. Both brothers have mild intellectual deficit -and had learning difficulties.
Whole exome sequencing was performed for both brothers and it showed likely pathogenic heterozygous nonsense variant *NM_006662.3:c.4780C>T* in *SRCAP* gene, *p.Gln1594**

Discussion. Our patients' phenotype and genetic testing data is compatible with developmental delay, hypotonia, musculoskeletal defects, behavioral abnormalities (*DEHMBA*). To this day, 33 cases are known. Despite different clinical situations, WES revealed correct diagnosis showing tendency of genotype first and reverse phenotype later. Cardiac and renal problems were not noted previously as part of the syndrome, so there is a chance that manifestation is due to other reason.
Conclusions. Broad genetic testing in isolated adult cases can discover unsuspected diagnosis that helps towards better clinical management.

SESSION 6 Syndrome Delineation

16:30: A CASE OF HYPOHIDROTIC ECTODERMAL DYSPLASIA AND HIRSCHPRUNG'S DISEASE WITH NO SEQUENCE VARIANTS AND COPY NUMBER VARIATIONS: HOW ABOUT WE DO A KARYOTYPE?

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Hypohidrotic ectodermal dysplasia (HED) and Hirschsprung's disease (HD) are both genetically heterogeneous disorders. HED is characterized by abnormal development of ectodermal tissues, particularly the skin, hair, nails, teeth, and sweat glands. HD is defined by the absence of ganglion cells in the Meissner's and Auerbach's plexuses of the distal rectum, with variable proximal extension.

We present the case of a 30-year-old woman, referred to our Medical Genetics Department due to clinical diagnoses of HED and HD. Her family and personal history were otherwise unremarkable. A skin biopsy performed at the age of 25 years revealed absence of skin appendages, namely hair follicles and eccrine and apocrine sebaceous glands.

On physical examination, she has sparse hair, missing teeth, decreased sudation, and eczema on the upper limbs.

She underwent whole-exome sequencing and MLPA for the *EDA*, *EDAR*, *EDARADD* and *WNT10A* genes, with normal results. Given the absence of a molecular diagnosis, we performed peripheral blood karyotype, which identified a *de novo* reciprocal and apparently balanced translocation between the long arm of one X chromosome and the long arm of one chromosome [46,XX,t(X;10)(q13;q11.2)dn]. This cytogenetic finding raised the possibility of *EDA* and *RET* disruption, respectively at Xq and 10q breakpoints.

Optical genomic mapping confirmed the result, showing that the breakpoint on the X chromosome is in intron 4 of the *EDA* gene (MIM *300451) and the breakpoint on chromosome 10 is in intron 1 of the *RET* gene (MIM *164761). This presumably results in the degradation of RNA through nonsense-mediated decay, preventing the production of otherwise non-functional truncated proteins. Loss-of-function variants in the *EDA* gene are associated with X-linked hypohidrotic ectodermal

dysplasia type I (MIM #305100), and loss-of-function variants in the *RET* gene are associated with susceptibility to Hirschsprung´s disease (MIM #142623).

This case illustrates the co-occurrence of two genetic disorders caused by a reciprocal and apparently balanced translocation, thus highlighting the importance of different diagnostic tools in the field of medical genetics. As far as we know, this is the first report of a translocation disrupting the *EDA* and *RET* genes, and the second of a translocation disrupting the *EDA* gene. The identification of this translocation modified genetic counselling and allowed the possibility of pre-implantation and prenatal diagnosis.

We show that classical methods, such as karyotyping, can still be crucial, and demonstrate the usefulness of optical genomic mapping. In the presence of a *de novo* balanced rearrangement, a pathogenic mechanism of gene disruption should be considered, particularly in cases with one or more genes of interest in the breakpoints.

16:45, BINDER PHENOTYPE WITH PALATAL EPULIS IN A FEMALE WITH CHROMOSOME 5P13.3P13.2 DUPLICATION

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A baby girl was born at 40+3 weeks gestation via spontaneous vaginal delivery at 3.66kg to non consanguineous healthy parents with no significant family history. Antenatal scans were normal but the face was not fully visualised. No resuscitation was required at birth, but the baby was noted to have a depressed nose, flattening of the external nose with a shortened columella and widened nasal alae. She had a soft mass on the hard palate without any associated underlying cleft. Due to feeding difficulties related to the mass, the baby was admitted to the neonatal unit. Intra-orally, a pedunculated hard palate epulis was found at the upper alveolar margin., approximately 2x3cm, which was firm but did not communicate with the nasal cavity or extend into the soft palate and surgical excision followed. The mass was found to be soft and non-vascular. At age 11 months she is healthy and developing normally. Histopathology of the palatal mass showed an eroded polypoidal lesion with overlying squamous mucosa. The polyp had a core of foamy-appearing cells with uniformed small round nuclei in keeping with a granular cell tumour.

A microarray showed a 2.4Mb paternally inherited duplication on chromosome 5p13.3p13.2 (33282207-35686157) hg 20 containing 25 genes; *ADAMTS12, AGXT2, AMACR, BRIX1, C1QTNF3, C1QTNF3-AMACR, DNAJC21, FHP2, GUSBP18, LINC02160, PRLR, RAD1, RAI14, RAI14-DT, RNU6-923P, RNU7-130P, RPL21P54, RXFP3, SLC45A2, SPEF2, TARS1, TARS1-DT, TOMM40P3, TTC23L, TTC23L-AS1, 15 protein coding, 7 disease associated (AGXT2, AMACR, DNAJC21, PRLR, SLC45A2, SPEF2 and TARS1),* none are associated with a phenotype of facial or palatal abnormalities nor a phenotype resulting from triplosensitivity. Her father is phenotypically normal and he has no relevant family history of either Binder syndrome or an epilus. Two similar copy number variants (CNVs) are present in Gnomad at low frequency. Within Decipher there are two cases with over lapping duplications associated with a depressed nasal bridge and a short nose. One (394282) with an abnormal nasal septum morphology (but a much larger duplication with a 1.08 Mb overlap; overlapping genes include AMACR, SLC45A2 and TARS1). Literature review revealed a case report describing an older girl with Binder phenotype (no epilus) and a marker chromosome 5*. Our smaller CNV completely overlapped with the larger marker chromosome in this child.
The genetic basis of Binder is unclear and no doubt heterogeneous. The phenotype in our patient is not identical as Hadzsiev's case (no epilus) and the fact that the father of our patient has no phenotype suggests this finding might be non contributory but as it is not possible to exclude possible causality recurrence risk remains slightly higher.
*Hadzsiev K, Dávid D, Szabó G., Czakó, M, Melegh B. & Kosztolanyi G. 2014. Partial trisomy of the pericentromeric region of chromosome 5 in a girl with Binder phenotype. *Cytogenet Genome Res,* 144**,** 190-5.

17:00: CHROMOSOME 17Q12 DELETION AND DUPLICATION IN THE IRISH POPULATION

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Background: The recurrent chromosomal region 17q12 is linked to diverse clinical manifestations, particularly neurodevelopmental issues and organ-specific abnormalities. Deletions of 17q12 are strongly associated with renal and genitourinary anomalies, as well as maturity-onset diabetes of the young type 5. In contrast, duplications exhibit variable phenotype ranging from normal to severe intellectual disabilities, developmental delays, and neuropsychiatric conditions.
Aim: This study explores the clinical phenotypes associated with 17q12 deletions and duplications in an Irish cohort.

Methods: 36 cases were identified through the cytogenetic and clinical database of the Department of Clinical Genetics, Children's Health Ireland, searching between 2013 and 2024: 20 with deletions and 16 with duplications. Array comparative genomic hybridization (Array-CGH) and next-generation sequencing-based copy number variant (CNV) analysis were utilized. Platforms included 120kb and 180kb CGH arrays (Agilent) and Illumina NovaSeq6000. Ethical approval was obtained (REC-503-24).

Results: Findings showed that 75% of deletion cases had antenatal findings, predominantly renal anomalies (85%), compared to only one duplication case with antenatal findings. Developmental delays were more pronounced in duplications than deletions, with significant differences in gross motor, fine motor, and speech delays. Neurodiversity and intellectual disabilities were observed in both groups, while more severe autism appeared more frequently with deletions, influencing school placement. Parental testing revealed that 80% of duplications were inherited compared to only 6% of deletions and parental phenotype were explored respectively.

Conclusion: This study highlights the multisystem and neurodevelopmental impact of 17q12 deletions and duplications. It also emphasizes the importance of parental segregation studies in guiding clinical management.

17:15: NEW POSSIBILITES OF MANAGEMENT WITH BEHAVIORAL PHENOTYPE IN PATIENTS WITH 20Q13.33 MICRODELETION ASSOCIATED WITH 17Q25.3 MICRODUPLICATION.

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We present a 10.5-year-old female patient with global developmental delay, atypical autism, stereotyped behaviors and sleep-wake rhythm disorders caused by an unbalanced chromosomal aberration (dup 17q25.1q25.3, del 20q13.33) inherited from her father with a balanced 17;20 translocation with breakpoints corresponding to the changes found in the patient.
The patient is a child from the first pregnancy complicated by EPH-gestosis and the need for a cesarean section. The perinatal period was complicated by: detection of complex heart defect - multi VSD, ASD, PDA, respiratory failure, seizures, aspiration pneumonia, feeding disorders. Dysmorphological assessment: high forehead, wide nasal bridge, hypertelorism, palpebral fissures set obliquely upwards, short eyebrow arches, with thinning in the distal 1/3 of the eyebrow arch, short and flat philtrum, narrow red lips, features of prognathism, slightly lower set auricles, lower set thumbs on both sides, with marked laxity of the interphalangeal joints, full transverse sulcus on both sides, flat-valgus feet, deepened lumbar lordosis, abnormal shape of the gluteal line.
Global developmental delay was noticed from early infancy: independent sitting at 13 months, independent walking at 3 years, currently using single words. Patient's behavioral phenotype includes: multiple motor stereotypes involving hands (hand flapping, flexing and spreading fingers, viewing hands in various positions in space) and exacerbated auto-aggressive behavior (punching forehead or thighs).
In the neurological picture: tonic focal seizures with behavioral arrest and subsequent muscle hypotonia observed since the age of 2, sleep disorders characterized by a shortening of the total sleep time with waking up around 4-5 a.m., as well as numerous awakenings during night sleep. In sequentially repeated EEG studies in sleep - epileptiform changes in the temporo-parietal-occipital areas, generalizing during sleep. Multiple failures of pharmacological treatment with noted excessive sleepiness after phenobarbital and valproic acid, deterioration of behavior and features of excessive agitation after each

attempt to introduce carbamazepine, despite the fact that carbamazepine use is dedicated to *CHRNA4*-related epilepsy, which causative gene is located in the patient's translocation region. based on the mapping of the aberration region found in the patient, it was decided to include resveratrol and nicotinamide riboside in the treatment, which modify the functioning of the neurotensin and sirtuin pathways disturbed by the dysfunction of the *NTSR1* and *SIRT7* genes located in the translocation region. The above procedure resulted in the most effective reduction in the intensity of auto-aggressive behaviors and improvement of the sleep pattern in the patient's history, which has been lasting for about last 6 months.
Our review of the literature, including 5 previously reported patients with the same chromosomal aberration, showed that our case is the first case of deterioration of seizure control during carbamazepine treatment and, at the same time, the first case of introducing resveratrol and nicotinamide riboside supplementation with a positive effect on the control of auto-aggressive behaviors, which may open new therapeutic perspectives in patients with changes in the 17q25.3 (*SIRT7*) and 20q13.33 (*NTSR1*) regions.

Friday 19th of September

SESSION 7 Unknowns

9:00: PATIENT WITH TETRAPLEGIA, MULTIPLE MALFORMATIONS AND DYSMORPHIC FEATURES WITHOUT A GENETIC DIAGNOSIS

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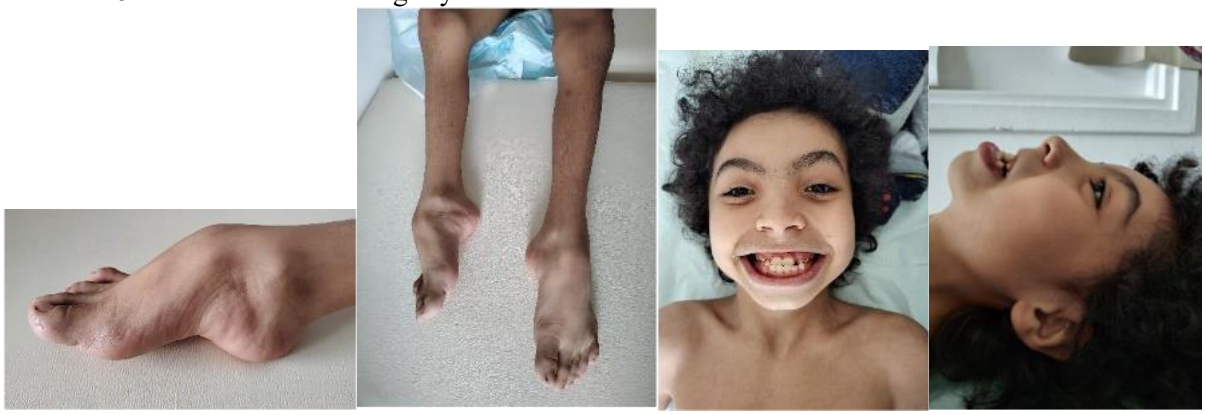
Our patient, a 9 years old boy has tetraplegia, hypotonia, arthrogryposis and multiple malformations.
He has horseshoe kidneys with reduced renal function.
His brain MRI revealed hypoplasia of the corpus callosum and posterior fossa and cyst of the septum pellucidum. No skeletal anomalies.
He presents with astigmatism, strabismus and peripapillary hyperpigmentation.
He has never acquired independent ambulation and sphincter control.
He eats pureed or slightly textured foods. He has a mild intellectual disability, spontaneous speech is present and he demonstrates an understanding of contextual language.
The patient has no hearing impairment.
His growth has consistently remained below the third percentile (-2DS).
Third-born at 37 weeks of gestational age, prenatal ultrasounds had already indicated a short femur.
From birth, he exhibited signs of hypotonia, feeding difficulties, dysmorphic facies, and he required ventilatory support in the neonatal period.
His mother, uncle and grandmother on the maternal side have congenital hearing loss.
On examination, he has class III malocclusion, genital hyperpigmentation. He has coarse facial features with thick, highly arched eyebrow, long palpebral fissures, mild palpebral ptosis, wide nasal brigde, smooth philtrum, macrostomia, thin upper lip and thick and everted lower lip, full cheeks, posteriorly rotated and low-set ears.
Array-CGH (60 Kb and 400kb), test for the GJB2, GJB6 and 12SrRNA mitochondrial genes associated with hearing loss were negative.
Exome sequencing (30 MB, trio analysis) also yielded negative results.
First clinical hypothesis was a PIEZO2-correlated disorder such as Marden-Walker syndrome, Arthrogryposis distal type 3 and type 5.

GestaltMatcher analysis identified as suggested disorders Developmental and epileptic encephalopathy 66, Pontocerebellar hypoplasia, Coffin-Siris syndrome, Mental retardation autosomal dominant 54 and Cornelia de Lange syndrome.



As the patient does not exhibit a consistent phenotype associated with these conditions and no pathogenic variants were found, none of the suspected diagnoses can be confirmed at this time.

9:10: UNDIAGNOSED CASE OF KABUKI-LIKE FACIAL DYSMORPHISM AND MOTOR DELAY IN A FEMALE TODDLER

Bianka AGARAJ [1],Tamar Ramishvili[2], Irakli Rtskhiladze[2], Nensi Dilo[1], Evis Nushi[1], Majlinda Toska[1]

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Background: Kabuki syndrome (KS) is a rare congenital disorder characterized by dysmorphic features, developmental delay, and multisystem involvement, most commonly caused by mutations in *KMT2D* or *KDM6A*. However, many patients with overlapping phenotypes remain undiagnosed due to inconclusive genetic results. We report an undiagnosed case of a 3-year-old female with Kabuki-like dysmorphism, persistent motor delay, and multiple variants of uncertain significance (VUS) identified on whole exome sequencing(WES).

Case Presentation:

Fig. 1: Visual representation of our patient dysmorphology generated by OpenAI, 2025

A 3-year-old female presented with persistent gross motor delay, manifested by inability to walk independently. While her cognitive and verbal skills are unaffected, physical examination revealed some distinguished dysmorphic features including long palpebral fissures, low-set and protruding ears, long eyelashes, thin and flat upper lips, highly arched eyebrows and hypotonia of the lower extremities. Growth percentiles were discordant: height at the 1st percentile, weight at the 53rd percentile, and head circumference at the 81st percentile. Brain MRI showed bilateral peritrigonal T2 hyperintensities, consistent with perinatal white matter injury while perinatal history was unremarkable (c-section delivery). Family history and echocardiography were non-contributory. Exome sequencing revealed 2 VUS: *KDM6A* c.108G>T (p.Glu36Asp), X-linked, associated with Kabuki syndrome type 2 and *WDR81* c.3447C>A (p.Ser1149Arg) and c.5344G>A (p.Gly1782Ser), both heterozygous and associated with autosomal recessive dysequilibrium syndrome. Additionally, AI-based GestaltMatcher facial analysis listed Kabuki syndrome as the 50th potential match.

Discussion: This case illustrates the diagnostic challenge of interpreting uncertain genetic variants in a patient with a syndromic phenotype. In low-resource settings such as Albania, where all diagnostic tests are paid out-of-pocket, clinical expertise and phenotype recognition often become the primary diagnostic tools. The KDM6A variant is absent from gnomAD and predicted to be deleterious by some tools but remains unreported in the literature. The WDR81 variants could be in trans, though the clinical picture is milder than typical cases. Female patients may also present with reduced penetrance, further complicating interpretation. Our aim is to identify similar cases and share experience on supportive management as a way to preserve mobility and reduce disease burden in undiagnosed neurodevelopmental syndromes.

Conclusion: We report an undiagnosed case of syndromic motor delay and dysmorphism with uncertain genetic correlates. This case underscores the value of phenotype-driven evaluation, functional variant assessment, and the importance of multidisciplinary care for children in the diagnostic gray zone.

9:20: UNDIAGNOSED SEVERE NEURODEVELOPMENTAL DISORDER IN A CHILD WITH INTELLECTUAL DISABILITY, EPILEPSY AND DYSMORPHIC FEATURES

Lisanna Põlluaas [1,2], Kristi Tael [1,2], Ülle Murumets [2], Katrin Õunap [1,2]

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Background: We report a patient with severe intellectual disability (ID), epilepsy, and dysmorphic features. Reanalysis of exome sequencing identified a previously undescribed variant in the *CDC42BPB* gene, which plays a role in cytoskeletal reorganization and cell migration in non-muscle cells. It functions as a downstream effector of *CDC42*, a gene associated with Takenouchi-Kosaki syndrome, characterized by delayed psychomotor development, ID, distinctive facial features, and abnormalities in multiple organ systems. In 2020, Chilton et al. reported 14 unrelated patients with variable clinical presentations, including ID, dysmorphic features, and numerous other health issues. All carried *de novo* heterozygous mutations in the *CDC42BPB* gene.

Materials and methods: Clinical metabolic investigations from serum and urine were normal. DNA was extracted from whole blood, libraries were prepared using DNA Prep with Exome 2.5 Enrichment kit and sequenced on Novaseq X Plus (Illumina). ES reanalysis was performed using the Broad Institute Seqr program. Parents were unavailable for familial segregation analysis.

Results: A 13-year-old girl presented with severe intellectual disability, epilepsy with abnormal EEG, stereotypies, restlessness, and toe walking. She began walking at 3 years and 10 months and has no speech. Additional issues include constipation, gastrostomy feeding due to reflexive vomiting, hypermetropia, and moderate astigmatism.
She was born to consanguineous parents from Syria from an uncomplicated pregnancy. One of her three siblings had epilepsy and died at the age of 1 year and 7 months.
Objectively, she was short and asthenic (weight: –2.25 SD; height: –5 SD; HC: –3 SD). Dysmorphic features included a broad nose, hypertelorism, mandibular prognathism, and an everted lower lip vermilion. The abdominal ultrasound was unremarkable. A gastric emptying scan showed delayed gastric emptying without evidence of obstruction. A brain MRI revealed several white matter lesions in the cerebral hemispheres of unclear etiology.
Initial ES was non-diagnostic. ES reanalysis identified a rare missense variant, NM_006035.4(CDC42BPB):c.773A>G (p.Tyr258Cys), which is absent from the gnomAD database (v4.1.0). According to the literature, this variant may be a candidate for diagnosis, though further validation is required.

Conclusion: We report the case of a 13-year-old girl with severe intellectual disability, epilepsy, and dysmorphic features without a confirmed genetic diagnosis. Exome sequencing reanalysis revealed a rare missense variant in the *CDC42BPB* gene, which has been associated with neurodevelopmental disorders. Further investigations, including long-read sequencing and multi-omic approaches, are needed to establish a definitive diagnosis and to assess whether the variant is disease-causing.

Funded by PRG2040.

9:30: A 4-YEAR OLD GIRL WITH CONGENITAL HEART DEFECT, EYE ANOMALIES AND SEVERE DEVELOPMENTAL DELAY.

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We present an undiagnosed case: a 4-year old female was first referred to genetic consultation at newborn age. She was born from third normal dizygotic twin pregnancy as a second twin at gestational age 37w+5 with birth weight 2750 g (10-25th centile), length 47 cm (10-25th centile), and HC 32 cm (10th centile). Apgar score 7/7/8.

After birth heart defects were diagnosed - hemodynamically relevant *ductus arteriosus* and a small muscular ventricular septal defect. She also had microphtalmia of the right eye, bilateral chorioretinal coloboma, and submucosal cleft palate. Her phenotype showed microretrognathia, hypertelorism and very high arched palate. She had severe muscular hypotonia and hyperlaxicity of joints, and feeding difficulties.

Family history: she has elder sister and brother, twin sister and younger brother, who are all healthy. Her father´s sister died in infancy due to congenital heart defect.

At one year of age, she presented failure to thrive (<3rd centiles), clinically CHARGE syndrome was suspected: she had coloboma, cranial nerve dysfunction, submucosal cleft palate, congenital heart defect, short stature, and developmental delay. Following investigations were performed: brain MRT showed bilateral colobomas, high arched palate, otherwise normal findings; EEG was normal, no epileptic activity. Genetic testing: chromosomal microarray showed normal karyotype, whole exome sequencing trio-analysis without any pathological findings; mtDNA analysis also normal findings.

At 3 years 7 months, her height was 84 cm (-3.5 SD), weight 9.9 kg (-3 SD), HC 46 cm (-3 SD), her motor development was severely delayed: head control was still a bit unstable, she has gained four-point support, she was slowly learning to eat soft chunky food. She only has little sense of light, but no vision. She has one understandable word “mommy”. She was diagnosed with growth hormone deficiency and gets treatment.

This case remains without a causal diagnosis that could offer an appropriate genetic counselling and a better surveillance to the patient and her family. By presenting this case, we hope that discussion can bring us closer to a genetic diagnosis.
Funding: PRG2040

9:40 AN UNDIAGNOSED 11-YEAR-OLD GIRL WITH PRENATAL VOLVULUS AND INTESTINAL PERFORATION, BRAIN MALFORMATIONS, DYSMORPHISMS AND SEVERE DEVELOPMENTAL DELAY: A LONG-OPEN CASE

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Here we present the case of an undiagnosed 11-year-old girl with severe global developmental delay and cerebral malformations, who was referred to our clinic for definition of recurrency risks due to the mother being pregnant.
A suspicion of a genetic condition was already present when the prenatal ultrasound at 20 weeks highlighted multiple bilateral choroid plexus cysts, slight enlargement of the renal pelvises and rounding of the caudal part of the corpus callosum. Karyotype analysis and array-CGH were performed on amniotic fluid with no pathological findings. The patient was born at 31 weeks through urgent caesarean section due to fetal intestinal perforation with stained amniotic fluid. She was then hospitalized for two months in neonatal ICU, undergoing surgery for middle ileal volvulus with numerous adhesions. Brain MRI highlighted cranial asymmetry due to flattening of the theca in the left temporoparietal region and diffuse enlargement of the cisterns of the base and of the liquor spaces, while skeletal X-rays could not

visualize cranial sutures and found diffuse reduction in bone density and irregular appearance of the metaphysis of the long bones.
In the following years, the patient manifested global developmental delay and moderate-severe autism spectrum disorder. EEG highlighted epileptiform activity, while brain MRI found white matter hypomyelination. She also had recurrent lower airways infections. During infancy, the family referred to different clinics for genetic consultation, but no diagnosis was reached.
The patient was referred to our clinic at 11 years of age. Family history was uneventful: she has a healthy 13-year-old sister, and the current pregnancy of the mother showed no pathological findings. Clinical examination highlighted craniofacial asymmetry, monolateral ptosis, highly arched eyebrow, low hanging columella, wide nasal ridge, high palate and long fingers. Exome sequencing of the trio resulted negative. The case was thus referred for genome sequencing in a research context, the results of which are still pending.
In conclusion, we present an unresolved syndromic case under medical scrutiny since the prenatal period. We would gladly accept any suggestion useful for solving this case.

1,2 - Asymmetry of the face, left eye ptosis, arched eyebrows, wide nasal ridge, low hanging columella, Greek helmet profile.

9:50 GENETICALLY UNSOLVED CASE OF CONGENITAL AORTIC VALVE ANOMALY, PROGRESSIVE SCOLIOSIS AND FINGER DEFORMITIES

10:00: MULTIDIMENSIONAL UNCERTAINTY IN THE DIAGNOSTICS OF FAMILIAL DEVELOPMENTAL DISORDER – A CASE OF POSSIBLE DOMINANTLY INHERITED MYT1L-RELATED NEURODEVELOPMENTAL SYNDROME

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[3] Department of Pediatrics, Institute of Clinical Medicine, University of Tartu, Tartu, Estonia
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Introduction: In the era of trio-based exome sequencing, inherited variants in dominant genes are often deprioritized if transmitted from an apparently unaffected parent. However, uncertain or subtle parental phenotypes may obscure true variant pathogenicity and complicate diagnostic interpretation.

Case: We report a 9-year-old male born at term (37 weeks, Apgar 8/9/9). Early motor development was age-appropriate, but speech development was significantly delayed. He was diagnosed at the age of seven years with mild intellectual disability (F70.0). At the age of six years, he was diagnosed with self-limited epilepsy with autonomic seizures, and his seizures are well controlled by lamotrigine. At the most recent evaluation, his anthropometric measures were within normal range: weight 35 kg (+0.5 SD), height 135.5 cm (−0.5 SD), head circumference 52.5 cm (−1 SD), and BMI 19.6 (+1.3 SD). Dysmorphic features included prognathism, malocclusion (posterior upper teeth), mild right divergent strabismus, high forehead, wide nasal bridge and tip, thin upper lip, prominent funnel-shaped ears, mild fifth finger clinodactyly, and joint hypermobility. Dental development was delayed by ~2 years, with absent anterior permanent tooth buds. Face2Gene and GestaltMatcher programs did not give any significant diagnostic clues.
Family history was notable: the mother had received special education, and also several paternal relatives reportedly had learning difficulties and/or seizures. The patient's younger brother has normal development. Prior genetic testing (NGS panel, CMA, *FMR1*, *DMPK*) was non-diagnostic, except for an incidental finding of maternally inherited *BRCA1* pathogenic deletion. Trio exome sequencing revealed no de novo or recessive variants explaining the phenotype. However, a maternally inherited missense variant in *MYT1L* was identified: NM_001303052.2:c.1909G>A, p.(Glu637Lys). This variant is absent from ClinVar and gnomAD, but is predicted to be deleterious by multiple *in silico* tools (MetaRNN, CADD, AlphaMissense, PrimateAI). Pathogenic variants in *MYT1L* are associated with autosomal dominant neurodevelopmental disorders, often with nonspecific features and variable expressivity (OMIM 616521).

Discussion: This case highlights several diagnostic challenges: (1) the variant is currently classified as of uncertain significance, despite strong computational support; (2) the phenotype of the carrier mother is insufficiently characterized; and (3) *MYT1L*-related and other similar disorders often lack distinctive clinical features, complicating genotype-phenotype correlation. This case underscores the evolving complexity of interpreting inherited variants in dominant genes, especially when parental phenotyping is ambiguous and clinical syndromes are nonspecific.

Funding: PSG774, PRG2040

10:10: WHEN WHOLE GENOME SEQUENCING IS NOT THE MAGIC SOLUTION: AN UNSOLVED FAMILIAL CASE OF NEURODEVELOPMENTAL DISORDER AND FACIAL DYSMORPHISM

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1: Department of Genetics, Mongi Slim hospital, La Marsa, Tunis Tunisia.
2: Research laboratory « santé mère enfant » LR22SP01, Tunis, Tunisia.
3: Human genetics laboratory, LR99ES10- Faculty of Medicine of Tunis, University of Tunis El Manar, Tunis, Tunisia.

Whole-genome sequencing (WGS) has become a powerful tool in the diagnosis of rare diseases, offering a more comprehensive approach than targeted methods. By examining the entire genome, WGS significantly increases the chance of identifying the genetic cause in neurodevelopmental disorders and congenital malformations, even in cases where prior genetic testing has been inconclusive.
We present the case of a 9-year-old girl referred for facial dysmorphism and neurodevelopmental disorder, including motor and language delay and intellectual disability.
The proband was born from healthy related parents and uneventfull pregnancy with normal birth measurements.

On physical examination, both height and weight were within the normal range. Facial dysmorphia was made of a long face, narrow forehead, hypertelorism, upslanting palpebral fissures, strabismus, long and smooth philtrum, and thick everted lower lip. No limb anomalies or joint laxity were noted, except for pes planus and hallux valgus. Family history revealed the same clinical presentation in two female siblings. Clinical exome analysis performed on the first sibling was normal, as was chromosomal microarray analysis carried out on the second sibling.
The molecular investigation in our proband was performed by WGS and revealed two variants of uncertain significance at the homozygous state in two genes: the first variant was in the *XYLT1* gene (NM_022166.4:c.1764+1555G>C). Biallelic variants in *XYLT1* are associated with Desbuquois dysplasia 2, a severe condition characterized by profound dwarfism, joint hypermobility with multiple dislocations of large joints, unique vertebral and metaphyseal anomalies and flat face with prominent eyes.
The second variant was found in the *VPS35L* gene (NM_020314.7:c.385A>G). Biallelic variants in this gene are associated with Ritscher-Schinzel syndrome-3, characterized by cranio-cerebello-cardiac anomalies and severe postnatal growth restriction, as well as complicated skeletal malformations, including vertebral body hypoossification, sternal aplasia, and chondrodysplasia punctata. Other features include developmental delay, ocular anomalies, periventricular nodular heterotopia, and proteinuria.
Therefore, neither of the genetic findings in WGS could explain the clinical findings in our patient. Despite a long clinical odyssey and the use of various new-generation techniques, our family remains without a diagnosis. This case highlights the need of further deep phenotyping in the affected sibs to refine the genotype-phenotype correlation.

10:20: UNDIAGNOSED CASE OF A 2- YEAR- OLD WITH SMALL TERMINAL PHALANGES AND BOWEL ATRESIA

Y. Woon, A. Hickey, S.A. Lynch[1]

1. Department of Clinical Genetics, Children's Health Ireland at Crumlin, Ireland

Background: We report a 2-year-old boy referred with shortening of the terminal phalanges in both hands and feet. On imaging, there is absent right 4th and 5th distal phalanges and left 3rd and 4th phalanges of both hands and absent distal phalanx of both 2nd toes. He has small distal phalanges of both big toes. He had multiple intestinal atresia requiring abdominal surgery after birth. He also has unilateral talipes, requiring both casting and surgical management. Development is appropriate with good hand function. His height is under the 0.4th centile and his mother describes a "stocky build" similar to his father. A half-sister underwent excision of an osteochondroma at age six.

Aim: To highlight the multisystemic features in this child and explore potential unifying diagnoses.

Methods: Microarray was normal. Trioexome sequencing identified a heterozygous paternal variant in *FLNB* gene inherited from his healthy father. This variant is associated with a recessive phenotype only & the phenotype does not fit that seen in our patient. The father (not seen) is reported to have no skeletal anomalies. Skeletal survey of the proband did not reveal any other anomalies apart from the digital findings.

Results: Multidisciplinary review raised the possibility of in utero vascular disruption as the underlying mechanism or microgastria-limb reduction defect syndrome. Maternal history included occasional cannabis use, but no other exposures were reported.

Conclusion: This case highlights a rare combination of digital, skeletal and gastrointestinal anomalies without a unifying diagnosis. Wider discussion may clarify whether this reflects atypical vascular disruption.

SESSION 8 Syndrome Delineation

11:00: *Invited Talk, Jan Deprest, Predicting and reversing the natural history of spina bifida*

11:45: EXPANDING THE CLINICAL SPECTRUM OF RITSCHER-SCHINZEL SYNDROME: A NEWBORN CASE WITH A NOVEL BIALLELIC VPS35L VARIANT

12:00: A NOVEL CASE OF MARFANOID-PROGEROID-LIPODYSTROPHY SYNDROME, A RARE, CLINICALLY RECOGNIZABLE FBN1-RELATED

Niels Vos[1,2,*], Quinten Waisfisz[1,2], Mariëlle Alders[1,2], Alessandra Maugeri[1,2], Saskia Maas[1,2]

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Background: Marfanoid-progeroid-lipodystrophy syndrome (OMIM #616914) is a rare, autosomal dominant, *FBN1*-related disorder, caused by pathogenic variants in exon 64 of the *FBN1* gene. To date, only nine patients with Marfanoid-progeroid-lipodystrophy syndrome have been described. Marfanoid-progeroid-lipodystrophy syndrome is a rare, clinically recognizable *FBN1*-related disorder that is associated with clinical features of Marfan syndrome in combination with a facial phenotype that resembles lipodystrophy or progeroid disorders, yet without currently known other features of progeria or lipodystrophy.

Case description: Our case is a girl seen at our outpatient clinics at age 7 months. She was born prematurely (34 weeks and 4 days) after a further uneventful pregnancy. She had a good start and no hypotonia, but she did have neonatal feeding difficulties that required tube feeding. She had poor weight gain and rapid growth. A benign external hydrocephalus was discovered. Upon physical examination, scaphocephaly, large fontanelles, a prominent forehead, upslanted palpebral fissures, deep-set eyes with protrusion, a highly arched palate, micrognathia, arachnodactyly and hypermobility were noticed.

Results: Targeted sequencing of the *FBN1* gene revealed the heterozygous pathogenic variant: *FBN1*: Chr15(GRCh37):g.48704941C>T NM_000138.5:c.8052-1G>A p.?

Discussion: Clinically we suspected our case to have Marfanoid-progeroid-lipodystrophy syndrome. We identified a not previously described *de novo* heterozygous pathogenic variant in the *FBN1* gene. In line with previously described cases of Marfanoid-progeroid-lipodystrophy syndrome, this variant is expected to result in incorrect splicing, leading to loss of the last but one exon of the *FBN1* gene mRNA (exon 64), confirming our clinical suspicion. We would like to present the current case and her photo's with parents' permission and an overview of the previously described cases, in order to increase awareness of this syndrome.

12:15: WHEN FAMILIAR GENE TELLS A NEW STORY: A POTENTIAL NOVEL SYNDROME EMERGING FROM AN UNEXPECTED FBN1 DOSAGE EFFECT

Łukasz KĘPCZYŃSKI[1], Zuzanna KREPSZTUL-BACZEWSKA[1], Agata KUCIŃSKA[1], Katarzyna POŁATYŃSKA[2], Tadeusz KAŁUŻEWSKI[1], Marzena KOLASA-KICIŃSKA[3], Agnieszka KONOPKA[3], Izabela MICHAŁUS[3], Ewa STAROSTECKA[3], Renata STAWERSKA[3], Arkadiusz ZYGMUNT[3], Agnieszka GACH[1]

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Background: Geleophysic dysplasia and related acromelic dysplasias are rare skeletal disorders associated with short stature, characteristic facial features, and soft tissue anomalies. Mutations in *FBN1*, particularly gain-of-function variants in specific exons, have been implicated in these phenotypes. However, the role of *FBN1* gene dosage alterations, such as full-gene triplication, has not been established.

Clinical Presentation: A 6-year-old boy was referred for evaluation of short stature, failure to thrive, delayed psychomotor development, and significantly delayed bone age (estimated at 3 years at the chronological age of 5 years 10 months). He exhibited disproportionate short stature (height 107 cm, <3rd percentile), shortened long bones, idiopathic toe walking, and calf hypertrophy. Facial dysmorphism included a round full face, mild epicanthal folds, short nose, and upturned corners of the mouth. He was born at term (40 weeks) via cesarean section due to lack of labor progression. Birth weight was 2970 g, with an Apgar score of 9. Family history revealed maternal short stature and long bone shortening without prior genetic evaluation.

Genetic Investigations: MLPA analysis for *SHOX* (P018) was normal. Singleton exome sequencing did not reveal pathogenic SNVs or indels, particularly in *FBN1*, *ADAMTSL2*, or *LTBP3*. However, exome-based CNV analysis identified a de novo 1.75 Mb triplication at 15q21.1–q21.2 [NC_000015.9:g.(48051986_49800556)trp], encompassing 18 genes, including the full coding region of *FBN1*.

Conclusion: While gain-of-function mutations in FBN1 exons 37-38 and 41-42 are known to cause stiff skin syndrome and skeletal dysplasias (including geleophysic dysplasia), respectively. , *FBN1* gene amplification has not previously been described in this context. Given the phenotypic overlap and the absence of other pathogenic findings, we propose a novel gain-of-function mechanism driven by increased *FBN1* dosage. This case highlights the potential relevance of copy number gains in the differential diagnosis of geleophysic dysplasias and expands the known spectrum of *FBN1*-related disorders.

SESSION 9 AI-driven Syndrome Diagnosis

14:00: *Invited Talk, Algirdas Utkus, Reflections of congenital anomalies in Lithuanian mythological stories and legends*

14:45: IDENTIFYING FACIAL DYSMORPHISM AND FACIAL PHENOTYPES OF GENETIC DISORDERS BY MEANS OF FACE2GENE IN THE CONGOLESE COHORT OF DDD-AFRICA

Prince Makay[1,2,3], Gerrye Mubungu[1,2], Prosper Lukusa Tshilobo[1,2,3], Aimé Lumaka[1,2], Koenraad Devriendt[3]

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Facial dysmorphism facilitates reaching an etiological diagnosis in persons with developmental disorders (DD). However, dysmorphism evaluation is largely subjective. The different morphological background of African persons may hamper the recognition of dysmorphism and specific syndromes. We evaluated Face2Gene for both the recognition of facial dysmorphism (D-score) and identifying genetic syndromes in Congolese individuals with a DD, in the framework of DDD-Africa.
We evaluated 2D facial photographs of pediatric persons with a DD from the DR Congo (n=144) and Belgium (n=137) as being dysmorphic or not, by D-score analysis compared to clinical evaluation. The incidence of gestalt-defined dysmorphism was high: Congolese 48%, Belgian 41%. The D-score in the Congolese showed a PPV 71.1%, NPV 83.6%. The F1-score was 0.78. The k was 0.531 (0.395–0.666). In the Belgian cohort, PPV 63.5%, NPV 78.4%, F1-score 0.672. The k was 0.422 (0.270-0.574). There was no significant difference with age and sex. In these cohorts with a high incidence of facial dysmorphism, the agreement between gestalt evaluation and D-score was moderate.
In 147 individuals evaluated by exome sequencing, a diagnosis was reached 63 individuals, representing 57 different conditions. The presence of clinically defined dysmorphism was associated with a higher chance of reaching a diagnosis (p=0.011; OR 3.714 (95% C.I. 1.35-10.21). A positive D-score was not associated with a chance of reaching a diagnosis (p=0.813; OR 1.137 (95% CI 0.39-3.30).
A 'mask' was available on Face2Gene for 33 patients, representing 28 conditions. Two patients had a dual diagnosis. In 21 patients (63.6%), Face2Gene returned the diagnosis within the first 10 matches. 87% of individuals with a Face2Gene match were clinically dysmorphic, compared to 70% of those where Face2Gene did not recognize the disorder without significant difference (p=0.251). Face2Gene performs well in dysmorphic Congolese individuals for which Face2Gene has a mask.
Key words: Face2Gene, D-score, Dysmorphism, Genetic disorder, Congolese, DDD-Africa.

15:00 ADVANCING GENOTYPE-PHENOTYPE ANALYSIS THROUGH 3D FACIAL MORPHOMETRY: INSIGHTS FROM CRI-DU-CHAT SYNDROME

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Facial dysmorphism is present in many monogenic disorders and an accurate assessment of dysmorphic features contributes to diagnostics, nosology and variant interpretation. Despite efforts towards standardization, comprehensively assessing the complex facial shape transformations associated with specific syndromes remains challenging. In this work, we propose 3D morphometric techniques to overcome these limitations, utilizing Cri-du-Chat syndrome (CdCS) as a model.
We used 3D facial photos of 24 individuals with CdCS, 4540 unaffected controls and 5 individuals with rare 5p15.33-15.32 deletions to objectively assess individual and recurring dysmorphic features using facial signatures. We applied two different methods to account for age- and sex related facial variation, quantified within- and between-group phenotypic variation and used morphometric tools to study genotype-phenotype correlations in CdCS.
We found that the facial phenotype in CdCS differs from controls in a highly consistent direction, but with varying magnitude of that effect. We demonstrated an evolving facial phenotype with age and identified drivers of atypical phenotypic features. 5p15.33-15.32 heterozygotes have non-specific dysmorphic features that are objectively different from those in CdCS, delineating multiple critical regions for facial dysmorphism on chromosome 5p.
This work explores 3D morphometric techniques for a quantitative assessment of facial features that is complementary to the standard clinical assessment. It provides insights into the genetics of facial shape

and shows the potential of 3D morphometric techniques to assist clinicians and researchers in diagnostics, variant interpretation, and syndrome nosology.

15:15, FROM FACE TO FUNCTION: SEC24C DEFICIENCY MIMICS GPI-ANCHOR BIOSYNTHESIS DISORDERS

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Background: *SEC24C* encodes a cargo-selective COP II subunit required for ER export of glycosyl-phosphatidylinositol-anchored proteins (GPI-APs). To date, a single case from a consanguineous pedigree with biallelic loss-of-function variants has defined a provisional clinical entity characterised by congenital cataracts, epileptic encephalopathy, dyserythropoietic anaemia and defective protein trafficking. We describe a child with biallelic single-amino-acid changes in *SEC24C* who mirrors the clinical and facial pattern of the only previously reported family, thereby strengthening the evidence for a human *SEC24C* disorder and illustrating how AI-based facial analysis can direct gene discovery

Methods: Comprehensive neurological, ophthalmological, haematological and neuro-imaging examinations were followed by AI-driven facial phenotyping with GestaltMatcher, which prompted targeted analysis of genes involved in GPI-anchored protein (GPI-AP) transport. Trio exome sequencing revealed two rare variants in *SEC24C*: a maternally inherited in-frame deletion (p.Ser156del) within the cargo-binding loop and a missense substitution (p.Arg1040Gln) in the C-terminal domain, maternally inherited. Pathophysiological characterization via peripheral-blood flow cytometry of CD55, CD59, CD73 and FLAER as well as plasma N-glycan profiling are in progress.

Results: The child displays global developmental delay, pronounced hypotonia with absent reflexes, unilateral sensorineural hearing impairment, optic atrophy with nystagmus and strabismus, plagiocephaly, diffuse hypomyelination and a thin corpus callosum on MRI, gingival hypertrophy with a tented upper lip, and mild anaemia. At three years no cataract is detectable, suggesting either age-dependent expression or an attenuated effect of the missense allele relative to the previously reported loss-of-function genotype.

Conclusion: AI-driven facial-gestalt analysis steered us toward *SEC24C* as the prime suspect in this second, unrelated patient, allowing rapid identification of two biallelic single-amino-acid variants. The concordant clinical and craniofacial overlap with the original *SEC24C* family—and with classic GPI-anchor disorders—strengthens the gene's candidacy for a human ER-to-Golgi protein-trafficking syndrome that phenocopies GPI-anchor deficiencies. Upcoming clinical analysis, flow-cytometric GPI-AP profiling and plasma N-glycan analysis will define the pathogenicity of these alleles and further refine the emerging *SEC24C* phenotype-genotype relationship.

SESSION 10 Dual Diagnosis or Phenotypic expansion?

16:00: A PATIENT WITH NSD2-RELATED NEURODEVELOPMENTAL DISORDER WITH UNEXPLAINED JOINT HYPERMOTILITY AND RECURRENT URINARY TRACT INFECTIONS

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The *NSD2* gene encodes a histone methyltransferase involved in chromatin remodeling and gene expression regulation. Pathogenic monoallelic variants in *NSD2* have recently been associated with Rauch-Steindl syndrome (#OMIM 619695), a neurodevelopmental disorder with variable expressivity and incomplete penetrance. Of note, the *NSD2* gene is considered critical for the 4p deletion causing Wolf-Hirschhorn syndrome (WHS) phenotype.
We report the case of a 20-year-old male patient presenting with borderline intellectual functioning (IQ 85), dyspraxia, strabismus, and socio-relational difficulties since early childhood. Neuromotor development was characterized by neonatal hypotonia and early fatigue. He never had seizures and brain MRI was normal. Facial dysmorphisms at clinical examination included prominent forehead, microretrognathia, low-set and posteriorly rotated ears, hypertelorism, strabismus, full lips, bilateral camptodactyly of the IV finger, monolateral single palmar crease, dental anomalies (lateral incisor agenesis and enamel dysplasia). He also presented with joint hypermobility (Beighton score 6/9) with several episodes of shoulder and knee subluxations requiring surgery, stretch marks on the abdomen, lumbar region and axillary fold, scoliosis, genu recurvatum, recurrent upper airways and urinary tract infections without urinary tract malformations, mild hepatic steatosis, and features consistent with mast cell activation syndrome (MCAS), confirmed by bone marrow biopsy.
Exome sequencing (ES) had been requested by a pediatric neurologist prior to consultation with the clinical geneticist and had identified a *de novo* heterozygous nonsense variant in NSD2 (NM_001042424.3): c.3412C>T; (p.Arg1138Ter), currently classified as pathogenic.
The result of ES explained the neurodevelopmental phenotype, but did not justify the hyperlaxity for which the patient had initially been referred to the clinic nor the recurrent urinary infections since childhood. After consultation with the clinical genetics department and post-test counselling regarding ES results, the patient was referred for immunological evaluation to better understand his apparent predisposition to infections.
We are open to discussion regarding whether the unexplained phenotype should warrant further testing or whether it could be some yet undescribed association to the *NSD2*-phenotypic spectrum: hypogammaglobulinemia has been described in WHS patients and recent evidence in mouse models points to a role of NSD2 for innate humoral immunity and follicular helper T cell differentiation (Dobenecker et al, *FEBS Lett*. 2020; Long X et al, *J Exp Med*. 2020). A mild immunodeficiency might therefore be a feature associated to haploinsufficiency of NSD2 alone, even without the whole WHS 4p microdeletion.

16:15: OVERLAPPING PHENOTYPES IN A DUAL DIAGNOSIS: 1P36 DELETION AND KMT2E VARIANT

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Background: The co-occurrence of multiple genetic syndromes can lead to complex clinical and craniofacial phenotypes, complicating diagnosis and management. We report a female patient with

corpus callosum agenesis and a dual molecular diagnosis of 1p36 deletion syndrome and KMT2E-related neurodevelopmental disorder (O'Donnell-Luria-Rodan syndrome).

Case report: In an otherwise uneventful pregnancy, intrauterine growth restriction was suspected after 30 weeks of gestation. Detailed fetal ultrasound revealed agenesis of the corpus callosum, right ventricular dominance with mild hypertrophy, and a prominent moderator band. The female infant was born at 38 weeks of gestation, small for gestational age (weight 2280 g, 3rd percentile; length 45 cm, 4th percentile; head circumference 33 cm, 49th percentile), with Apgar scores of 9 and 9. Dysmorphic features included a sloping forehead, hypertelorism, broad nasal bridge with cleft tip, high-arched palate, long fingers, fifth finger clinodactyly, and overlapping toes. Postnatal neuroimaging with ultrasound, followed by MRI, confirmed the prenatal findings and additionally showed colpocephaly, frontotemporal pachygyria, an extra-axial lipoma, arachnoid cysts, and bilateral ventriculomegaly. After a focal febrile seizure, EEG showed focal epileptiform discharges and slow waves, leading to a diagnosis of epilepsy. Cardiac evaluation revealed a patent ductus arteriosus, suspected left ventricular noncompaction cardiomyopathy, and mild aortic valve regurgitation.

Genetic testing: Whole exome sequencing identified two clinically significant findings: a likely pathogenic heterozygous frameshift variant in the *KMT2E* gene (c.1780del, p.Arg594Glufs*52), associated with KMT2E-related neurodevelopmental disorder, and a pathogenic 6.2 Mb heterozygous deletion in 1p36.32–p36.22 (chr1:3102674–9307142), encompassing 68 genes, consistent with 1p36 deletion syndrome.

Discussion: The patient's features could result from either syndrome, highlighting the phenotypic overlap between them. Although the deleted region includes genes linked to microcephaly (e.g., *RERE, CDC42, SKI*), the patient showed relative macrocephaly, suggesting an atypical 1p36 deletion presentation. The *KMT2E* frameshift variant, typically linked to macrocephaly, may better explain the complex phenotype.

Conclusion: This case highlights the diagnostic complexity of multilocus genomic variation, where overlapping features from two distinct syndromes result in a blended phenotype. While 1p36 deletion syndrome could explain much of the clinical presentation, the additional *KMT2E* variant likely accounts for the atypical features. If the patient had undergone chromosomal microarray alone, a second single-gene disorder could have been overlooked. Therefore, a second diagnosis should always be considered, especially in cases with nonspecific clinical features or when the phenotype is more atypical than expected.

16:30: UNUSUAL SYNDROMIC PRESENTATION IN A CHILD WITH A NOVEL SIX1 VARIANT

Katarina VULIN[1,2], Ana Maria MEAŠIĆ[1,2], Ivona SANSOVIĆ[1,2], Leona MOROŽIN POHOVSKI[1,2], Ivana ĐAKOVIĆ[3], Ana TRIPALO BATOŠ[4], Ljubica ODAK[1,2]

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Background: The *SIX1* gene encodes a transcription factor critical for the development of the ear, the second branchial arch, and the kidney. Pathogenic variants in the *SIX1* gene are most commonly associated with branchio-oto-renal (BOR) spectrum disorders. We present a paediatric patient with a complex syndromic phenotype in whom clinical exome sequencing revealed a novel *SIX1* variant.

Case report: Our 10-year-old female patient was delivered at term via caesarean section, with a birth weight of 3590 grams, a length of 49 centimetres, and Apgar scores of 8 and 9 at one and five minutes, respectively. Multiple dysmorphic features were observed, including hypertelorism, a depressed nasal bridge, and bilateral auricular anomalies (a left-sided lop ear and a malformed right auricle with a fistula and a skin tag). Additionally, she presented with a cleft of the hard and soft palate. Audiological assessment revealed profound bilateral sensorineural hearing loss secondary to cochlear aplasia, accompanied by middle ear malformations and hypoplasia of the external auditory canals. Spina bifida occulta was also identified.
Cyanotic episodes began at 12 days of life. Despite a thorough diagnostic evaluation, no definitive aetiology was identified, and the episodes resolved spontaneously throughout infancy. At the age of two, the patient required cardiopulmonary resuscitation following an unexplained cyanotic episode. Extensive investigations again failed to identify a definitive underlying cause. At the age of four years, she experienced febrile seizures. Her cognitive development at age seven was normal, and she communicates effectively using sign language.
Family history revealed that a paternal half-brother died at the age of seven months due to sudden infant death syndrome. Following the birth of this patient, the mother experienced a spontaneous miscarriage at 14 weeks of gestation.

Methods and results: The clinical exome sequencing was performed using the TruSight One Sequencing Panel on the NextSeq500 platform (Illumina Inc., USA). This analysis identified a likely pathogenic, de novo missense variant in the *SIX1* gene c.520A>C, p.Asn174His, not previously reported in the literature. This was also confirmed by Sanger sequencing.

Conclusion: The identified novel *SIX1* variant expands the known genotypic spectrum of rare *SIX1*-related disorders. However, this variant does not fully explain the clinical presentation, which includes atypical features such as spina bifida occulta and unexplained cyanotic episodes. This suggests that additional genetic factors may be involved. Further genetic investigations are essential to better understand the complexity of this syndromic presentation.

Grants: This study was supported by CERRM, the Republic of Croatia, and the EU through ERDF, under grant agreement No. KK.01.1.1.01.0008, project “Reproductive and Regenerative Medicine - Exploring New Platforms and Potentials”.

16:45: A NOVEL FAMILIAL CASE OF THAUVIN-ROBINET-FAIVRE SYNDROME (TROFAS), PRESENTING WITH HEXADACTYLY AND ARTERIOVENOUS MALFORMATION.

Federica Ruscitti

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Thauvin-Robinet-Faivre syndrome (TROFAS, OMIM #617107) is a recently identified autosomal recessive disorder characterised by syndromic overgrowth, typically accompanied by facial dysmorphism, mild intellectual disability, variable congenital anomalies, and an increased risk of embryonic tumours. TROFAS results from homozygous or compound heterozygous variants in the *FIBP* gene, which encodes the intracellular binding protein for acidic fibroblast growth factor. This protein plays a role in the fibroblast growth factor (FGF) signalling pathway, which is involved in cell proliferation and contributes to the development of several structures, such as the nervous system, optic vesicles, and blood vessels.
To date, TROFAS has been described in eight patients from five families, three of which are of Turkish origin. In this report, we describe two additional Turkish siblings harbouring the previously reported homozygous c.412-3_415dup likely pathogenic variant in *FIBP*. Both presented with typical TROFAS features; however, the male sibling exhibited a more severe neurodevelopmental profile and additional

malformations, including hexadactyly and arteriovenous malformation, reported here for the first time in association with TROFAS.
A detailed clinical characterisation of these two new cases contributes to refining and expanding the phenotypic spectrum of TROFAS.

17:00: OUTCOMES OF PATIENTS WITH MITOCHONDRIAL DISEASE: A RETROSPECTIVE STUDY OF A COHORT OF 238 PATIENTS DIAGNOSED AND FOLLOWED AT NECKER-ENFANTS MALADES HOSPITAL

Antoine Pouzet[1], Claire Mayer[2], Claire Marine Berat[2], Agnès Rötig[3], Manuel Schiff[2]

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Introduction: Mitochondrial diseases are disorders of energy metabolism that affect oxidative phosphorylation. Their clinical presentation—particularly neurological, hepatic, or cardiac—along with the age of onset, can vary widely from one patient to another.

Objective: This study explores the initial clinical presentation and outcomes of patients with mitochondrial diseases.

Methods: We conducted a retrospective study of a cohort of 238 children diagnosed and followed at Necker-Enfants Malades Hospital. For each patient, the diagnosis of a mitochondrial disease was molecularly confirmed.

Results: In our cohort, the overall mortality rate was 45.3%. This rate varied significantly depending on the age at symptom onset. The mortality rate among children who presented with a neonatal onset was 65.4%, while patients who became symptomatic between ages 5 and 18 had a mortality rate of 7.7%, suggesting that earlier symptom onset is strongly associated with increased mortality risk. Neurological or neurodevelopmental presentations—such as Leigh syndrome, epilepsy, focal neurological symptoms, and psychomotor developmental delays with or without regression—were the most common initial manifestations.

Conclusions: These findings confirm the high morbidity and mortality associated with pediatric-onset mitochondrial diseases. Previous large pediatric cohorts have reported mortality rates ranging from 38% to 60%, depending notably on the age at onset and the nature of initial symptoms. These data highlight the importance of early symptomatic management and close monitoring of these patients' clinical status.

17:15: A NEW CASE OF SHORT STATURE, BRACHYDACTYLY, INTELLECTUAL DEVELOPMENTAL DISABILITY, AND SEIZURES (SBIDDS) SYNDROME IN A 27 YEAR OLD MALE OF SLAVIC ORIGIN

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Background: SBIDDS is a rare autosomal recessive genetic disorder caused by Arginine Methyltransferase 7 (PRMT7) disfunction. Apart from the most prominent manifestations (Short

stature, Brachydactyly, Intellectual Developmental Disability and Seizures; SBIDDS) it's characterized by craniofacial dysmorphism and obesity. According to ORPHANET, less than 15 cases of SBIDDS have been reported in the literature up to date.

Material and Methods: 27-year-old patient of Ukrainian origin, was born from the fourth pregnancy, after two pregnancies losses and healthy sister. There were no cases of neurodevelopmental or skeletal disorders in familial history. The patient was presented with absent speech, profound intellectual disability, generalized seizures, microcephaly, craniofacial anomalies, disproportionate short stature with short trunk, thoracic kyphoscoliosis, brachydactyly, but there wasn't obesity. Clinical Genetic Testing, CentoArray, WES (CENTOGENE) was done.

Results: A homozygous pathogenic variant of PRMT7 gene (c.820C>T) (p.(Arg274*) in exon 9 of PRMT7 gene was identified. It is classified as pathogenic both upon ClinVar and CENTOGENE's guidelines. Carrying of biallelic pathogenic PRMT7 variants now is consistent with a genetic diagnosis of autosomal recessive short stature, brachydactyly, intellectual developmental disability, and seizures; SBIDDS (OMIM: 617157). Although the patient's parents deny any consanguinity, the homozygous state of rare gene variant PRMT7(c.820C>T) (p.(Arg274*) in their son requires heterozygous carrier testing for other family members.

Conclusions: Genetic testing confirm the SBIDDS as a primary cause of neurodevelopmental delay and multiple skeletal anomalies in Ukrainian patient, that could be a 16th diagnosed case of this ultimately rare disease.

Saturday 20th of September

SESSION 11 Syndrome Delineation

9:00: FAMILIAL PRESENTATION OF NYSTAGMUS AND OPTIC ATROPHY IN NOONAN SYNDROME WITH LOOSE ANAGEN HAIR: A CASE STUDY OF MOTHER AND DAUGHTER WITH PPP1CB MUTATION

Maren Wenzel

Nystagmus and optic atrophy are rare but documented ocular manifestations in Noonan Syndrome (NS) and related RASopathies. In Noonan Syndrome with Loose Anagen Hair (NS-LAH), caused by SHOC2 mutations, optic nerve hypoplasia and nystagmus have been reported yet in a single case, suggesting a developmental disorder of the optic nerve (Gripp et al, 2016).
Here I present a mother and her daughter with Noonan Syndrome with Loose Anagen Hair (NS-LAH), caused by PPP1CB mutation, who both have nystagmus caused by optic nerve atrophy.
In addition, we are treating two unrelated patients with Noonan syndrome through PTPN11 mutation in our consultation, both of whom have optic atrophy.
Among NS patients with PTPN11 mutations, only one case of visual impairment due to optic nerve atrophy has been reported to the best of our knowledge. Five other patients are known with optic nerve head abnormalities like excavation or coloboma and one with optic nerve head paleness (van Trier et al, 2018).
In RASopathies overall, including Cardiofaciocutaneous Syndrome (CFCS), optic nerve hypoplasia and nystagmus are more frequently observed, particularly in patients with mutations in BRAF, KRAS, and MAP2K1/2 genes (Crincoli et al, 2023).
The presumed mechanism involves dysregulation of the RAS/MAPK pathway, which affects cellular proliferation and differentiation during development. This pathway's dysfunction may impair optic nerve development and contribute to nystagmus through disrupted neural signaling (Roberts et al, 2006).

Further research is needed to establish genotype-phenotype correlations and improve early diagnosis and management.

9:15: A NOVEL DE NOVO ZEB2 FRAMESHIFT VARIANT IN MOWAT-WILSON SYNDROME PRESENTING WITH UNICORONAL CRANIOSYNOSTOSIS

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Introduction: Mowat-Wilson syndrome (MWS, OMIM #235730) is a rare autosomal dominant disorder caused by heterozygous variants in the *ZEB2* gene (OMIM *605802*). *ZEB2* encodes a zinc finger transcription factor that functions as a Smad-interacting repressor and plays a key role in early embryonic development, especially in neural crest-derived tissues and the formation of the nervous system. The clinical picture of MWS includes global developmental delay, intellectual disability, epilepsy, multiple congenital anomalies (such as Hirschsprung disease and congenital heart defects), and characteristic craniofacial dysmorphism. Although unicoronal craniosynostosis has been described in MWS, it remains a rare finding within the clinical spectrum.

Case report: We report a case of a 3.5-year-old female patient, born from the first IVF-conceived twin pregnancy due to parental infertility. She was delivered by emergency cesarean section at 34 weeks of gestation, with a birth weight of 1770 g, length of 44 cm, head circumference of 29 cm, and Apgar scores of 10 at 1, 5, and 10 minutes. Postnatally, congenital heart defects were diagnosed, including a bicuspid aortic valve and a patent ductus arteriosus (PDA), surgically corrected in the second week of life. In addition, left-sided coronal craniosynostosis was diagnosed and treated in two stages: distractor placement and later removal with orbital correction. The patient showed global developmental delay: sitting at approximately 12 months, first steps at age 3, and no spoken language to date. ABR was normal. She had two febrile seizures; EEG was normal and epilepsy was excluded. Mild myopia and growth below the 3rd percentile were also noted. On physical examination, craniofacial dysmorphism was observed, including frontal bossing, facial asymmetry despite surgical intervention, and delayed closure of the anterior fontanelle.
Array comparative genomic hybridization (array CGH) using an Agilent 60K platform revealed no pathogenic copy number variants. Whole-exome sequencing identified a heterozygous pathogenic variant in the *ZEB2* gene: c.2730_2802del; p.(Met910Ilefs*43). Segregation analysis confirmed that the variant occurred de novo. This variant has not been reported in the medical literature or in disease-related variation databases. The overall clinical presentation, together with the molecular finding, led to the diagnosis of a rare genetic condition — Mowat-Wilson syndrome.

Conclusion: Our case expands the spectrum of genetic variants associated with Mowat-Wilson syndrome and supports the inclusion of unicoronal craniosynostosis among its rare craniofacial features.

9:30: KMT5B RELATED DISEASE MIMIC MARFAN SYNDROME

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KMT5B-related neurodevelopmental disorder is an autosomal dominant genetic disorder caused by pathogenic variant in the KMT5B gene that characterized by macrocephaly and intellectual disability.

Additional features include failure to thrive, unique facial and foot features, neurologic behavioural psychiatric problems, absent speech or language deficiency, and development delays with coordination difficulties. We have present one adult KMT5B related disease that initially thought to be Marfan Syndrome based on the clinical phenotype and aortopathy. Exome sequencing subsequently showed he has 2 denovo variants namely Heterozygous NM_017635.5(KMT5B):c.554_557del p.(Tyr185CysfsTer27) and Heterozygous NM_014491.4(FOXP2):c.163C>T p.(Gln55Ter). This ends the diagnostic odyssey for this gentlemen.

9:45: FROM ISOLATED MACROCRANIA TO A COMPLEX DIAGNOSIS: A NEWBORN WITH SNIDERS BLOK-CAMPEAU SYNDROME

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Chromatin remodeling disorders are a group of rare genetic syndromes caused by mutations in genes encoding proteins part of ATP-dependent chromatin-remodeling complexes that influence nucleosome positioning and accessibility of transcriptional machinery. Defects in these pathways can lead to disrupted gene expression profiles during embryogenesis and postnatal development, resulting in multisystem involvement. Clinically, these disorders often present with developmental delay, intellectual disability, hypotonia, autism spectrum features, macrocephaly or microcephaly, growth abnormalities, and subtle dysmorphic features. Snijders Blok–Campeau syndrome (SBCS, OMIM #618205) is one such disorder, caused by heterozygous pathogenic variants in the CHD3 gene, which encodes a component of the NuRD complex involved in transcriptional repression. Variants in *CHD3* impair neurodevelopment, with variable clinical expressivity.

We report a case of a female infant diagnosed with SBCS in early infancy. She was born following an IVF pregnancy for couple infertility. Non-invasive prenatal testing (NIPT) was low risk. At the second-trimester anatomy scan, biparietal diameter was >95th percentile and abdominal circumference was slightly above the upper limit of normal. She was born at 40+1 weeks of gestation by spontaneous vaginal delivery. Apgar scores were 8 at 1 and 5 minutes. Birth weight was 2990 g (-0.78 SDS), length 52 cm (+1.42 SDS), and head circumference 37 cm (+2.66 SDS), indicating macrocephaly. Axial hypotonia was noted at birth, prompting brain MRI and echocardiography, both normal. Neurodevelopmental evaluation showed mild immaturity. Feeding difficulties required logopedic intervention. Over subsequent months, growth was normal, with persistent head circumference above the 90th percentile. Neurodevelopmental milestones gradually improved, although hypotonia and mild developmental delay persisted, including delayed head control at 9 months.

At 4 months, genetic consultation revealed subtle dysmorphic features: micrognathia, low-set ears, pectus excavatum, flat nasal root, and axial hypotonia. Chromosomal microarray was normal. A targeted next-generation sequencing panel for macrocephaly and neurodevelopmental disorders identified a de novo heterozygous variant in *CHD3*: c.3682C>T (p.Arg1228Trp), classified as pathogenic due to its truncating effect on the protein. Based on clinical and genetic findings, a diagnosis of SBCS was made. The patient was referred for multidisciplinary follow-up including neuropsychiatric, neurodevelopmental, and speech therapy assessments.

This case emphasizes the importance of considering chromatin remodeling disorders such as SBCS in neonates presenting with macrocephaly and early hypotonia, even in the absence of major structural anomalies. Early genetic testing can facilitate timely diagnosis, enabling appropriate clinical follow-up and expanding the understanding of phenotypic variability associated with *CHD3* mutations.

10:00: EXPANDING THE PHENOTYPIC SPECTRUM OF RIBOSOMOPATHIES: A NOVEL RPL26 VARIANT IN A PATIENT WITH MULTIPLE CONGENITAL ANOMALIES

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Introduction: Diamond-Blackfan anemia (DBA) is a rare congenital disorder, originally described as an inherited bone marrow failure. DBA typically presents within the first year of life as moderate to severe anemia, with 30–50% of affected individuals also exhibiting growth retardation and congenital anomalies affecting the craniofacial region, upper limbs, and genitourinary tract. Most cases are caused by mutations in genes involved in ribosome biogenesis, with eight ribosomal protein genes accounting for 50–65% of cases. Although historically defined by its hematologic features, emerging evidence suggests a significant phenotypic variability, with some individuals carrying pathogenic variants in DBA-associated genes presenting without distinctive hematological features. To encompass this broader clinical spectrum, the term DBA syndrome has been adopted.

Case Presentation: We present the case of a 7-year-old girl referred for genetic evaluation due to multiple congenital anomalies and mild persistent leuko-neutropenia. Family history was notable for a paternal aunt who died of spina bifida at age one and a maternal cousin who died at birth from a complex heart defect. She was born at term with normal weight and head circumference but short length (SDS -2.37). Prenatal screenings were negative. Upon initial assessment, she presented hypoplasia of the right first digit and lateralization of the left first digit. Cardiac evaluation showed a double ventricular septal defect and an ostium secundum atrial septal defect, which underwent spontaneous closure. Additional findings included a cleft soft palate (surgically corrected at 9 months), crossed fused renal ectopia, and ocular anomalies (astigmatism and strabismus). Neurodevelopment was normal, with appropriate milestones and good school performance. At age 6, she developed severe thrombocytopenia following a viral illness, compatible with a diagnosis of immune thrombocytopenia. While platelet counts normalized, follow-up revealed persistent mild leuko-neutropenia. Fanconi anemia and other marrow failure syndromes were ruled out. Hemoglobin levels always remained consistently normal.

Genetic Findings: Initial genetic investigations resulted in a normal karyotype (46, XX), and negative targeted sequencing for *TBX5* and *SALL4* genes. CGH array identified two duplications of uncertain significance at Xp22.2p22.13 and 2p23.3, which were not considered to be linked to her phenotype. WES on the trio identified a maternally inherited missense variant in *RPL26*: c.344G>A (p.Arg115His). Notably, the mother is asymptomatic and has no history of hematological abnormalities. Further analyses showed elevated erythrocyte adenosine deaminase (eADA) levels and RNA profile via Bioanalyzer matching those seen in another patient with an RPL26 mutation, supporting the variant's likely pathogenicity.

Conclusion: RPL26 variants, initially identified in patients with classical DBA phenotypes, may also present predominantly with congenital malformations, most notably radial ray anomalies, and show minimal or no hematologic abnormalities, as seen in our patients. The pathogenicity of the identified variant is supported by elevated eADA activity and abnormal RNA Bioanalyzer profile. This case underscores the importance of maintaining a diagnostic suspicion of DBA syndrome when

characteristic multiple congenital anomalies are present, even in the absence of typical hematologic findings.

10:15: ATYPICAL PRESENTATION OF A PATHOGENIC CHD7 VARIANT IN A NON-DYSMORPHIC FAMILY

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Background: CHD7 gene pathogenic variants are classically linked to CHARGE syndrome, a multisystem disorder characterized by coloboma, heart defects, atresia of the choanae, growth and developmental delay, genital anomalies, and ear abnormalities or hypogonadotropic hypogonadism. Dysmorphic features and structural anomalies are typically prominent, being clinically recognisable syndrome. However, the phenotypic spectrum is broadening with the increasing use of genomic testing.

Case Presentation:We describe a non-consanguineous family with three affected siblings and mother, all carrying a pathogenic CHD7 variant, and presenting with variable, non-classical features of CHARGE syndrome, notably in the absence of dysmorphic traits.
The proband is a 17-year-old male who presented with progressive muscle weakness, shortness of breath over the past three years, sleep apnea, overweight (+2.6SD), and epilepsy. No prominent dysmorphic features were observed. Exome sequencing identified a likely pathogenic CHD7 missense variant and a variant of uncertain significance (VUS) in SMARCC2.
His half-sister has learning difficulties, conductive hearing loss, myopia, speech delay, and mild intellectual disability. She began walking at 14 months and has a height and weight above average (+2.6 SD). The same SMARCC2 variant was identified in her.
Another half-sister shows similar symptoms, including neurodevelopmental delay and shortness of breath, but without hearing loss. Both CHD7 and SMARCC2 variants were detected in this sibling.
The mother of all three siblings has epilepsy, right-sided conductive hearing loss, and memory issues. Genetic testing revealed that she carries both the CHD7 pathogenic variant and the SMARCC2 VUS.
To assess the pathogenicity of these variants, DNA methylation profiling was performed in the proband and older half-sister. The probands' sample was classified as CHD7 cases by all three published CHD7-related DNAm signatures using MethaDory tool, strongly supporting the diagnosis of a CHD7-related disorder and confirming the variant's pathogenic classification. This variant was also described in the literature in two cases with prominent scapulae, mild shoulder girdle weakness, only subtle dysmorphic features, epilepsy and developmental delay as de novo. In contrast, the sample did not match the two published methylation profiles associated with BAF complex disorders, arguing against a diagnosis of BAFopathy, in which belongs *SMARCC2* gene related disease.

Conclusion: This case highlights an atypical intrafamilial presentation of a pathogenic CHD7 variant, with absent dysmorphic features and predominant neurodevelopmental and respiratory symptoms. The absence of classical CHARGE syndrome traits underscores the need to consider CHD7 in broader diagnostic contexts. DNA methylation profiling proved instrumental in validating variant pathogenicity and clarifying the clinical interpretation in this complex case.

10:30: GENOTYPIC AND PHENOTYPIC SPECTRUM OF MENKE-HENNEKAM SYNDROME: TWO CASES WITH PATHOGENIC CREBBP VARIANTS

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Introduction: Menke-Hennekam syndrome (MHS) is a rare autosomal dominant neurodevelopmental disorder caused by pathogenic variants in the CREBBP gene, most commonly affecting exons 30 and 31. This condition is characterized by a spectrum of clinical manifestations including developmental delay, intellectual disability, broad spectrum of phenotypic features and multisystemic malformations. Despite increasing recognition, detailed genotype–phenotype correlations remain poorly defined. We report two cases with unique phenotypes.

Case Reports: Patient 1 is a 10 years old female who was healthy at birth but exhibited growth delay from early infancy. Her developmental milestones were delayed. EEG in 2019 revealed epileptiform activity, which resolved by 2021 without ongoing antiepileptic medication. Clinical examination revealed dysmorphic features such as a short neck, slanted eyebrows, epicanthal folds, hypertelorism, strabismus, short palpebral fissures, a rounded nasal tip, coarse facial features and slightly rotated ears, clinodactyly of the fifth finger; the patient showed short stature (<3rd %ile), average weight (~25th–50th %ile), and significantly reduced head circumference (<1st %ile). Whole exome sequencing (WES) revealed a likely pathogenic heterozygous CREBBP variant: NM_004380.3:c.5123T>C(p.Cys1708Arg) located in exon 30. aCGH: No pathogenic copy number variants. Patient 2 is a 11 years old male, with a history of feeding difficulties, cryptorchidism surgery, recurrent infections, and behavioral disturbances. He exhibited severe developmental delay, diagnosed with profound intellectual disability and atypical autism. Regression episodes occurred during illnesses. Phenotypically, he presented with a narrow forehead, upslanting palpebral fissures, almond-shaped eyes, low-set ears, midface hypoplasia, a wide mouth with downturned corners, dental anomalies, and long fingers with wide palms. The patient exhibited above-average height and weight (both 75th–85th %ile) with a markedly reduced head circumference (<3rd %ile). WES revealed a pathogenic heterozygous CREBBP variant: NM_004380.3:c.5614A>G (p.Met1872Val) located in exon 31. aCGH: No pathogenic copy number variants as well.

Discussion: These two cases exemplify the phenotypic variability associated with different pathogenic CREBBP variants. Both patients display developmental delay and dysmorphic features, though the male patient exhibits a more severe neurodevelopmental and behavioral phenotype. Both of the identified variants have been previously reported as a recurrent de novo variant in individuals with variable developmental delay, intellectual disability, short stature and/or microcephaly. Both are consistent with the MHS phenotype described in the literature.

Conclusion: Our case reports expand the clinical spectrum of Menke-Hennekam syndrome and emphasize the importance of whole exome sequencing in diagnosis. Detailed clinical characterization and reporting of additional cases is essential for improving genotype–phenotype correlations and guiding management strategies.

10:45 EXPANDING THE CLINICAL PHENOTYPE OF TRAF7 GERMLINE MUTATION – DETAILED DESCRIPTION OF PATIENT WITH CAFDADD SYNDROME

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Introduction: CAFDADD - cardiac, facial and digital anomalies with developmental delay is a very rare genetic disorder with clinical features overlapping in some patients those of OHDO syndrome as blepharophimosis and ptosis, cleft palate, deafness, heart defect, hypotonia. Some patients have epilepsy, ocular/auricular defects and enlarged ventricles.
Patients and methods: We present clinical evaluation of one patient earlier suspected to have OHDO syndrome. The mutation analysis in these patients was performed using whole exome sequencing.

Results: Patient had abnormal prenatal ultrasound finding – high nuchal translucency (3,7 mm >95c) and heart defect (VSD). Postnatal findings were hypotonia, speech delay, autism spectrum disorder, deafness, ptosis and blepharophimosis, cleft palate, small teeth, ribs defects, wildly located nipples, mVSD, supernumerary spleen, umbilical hernia, abnormal skull shape, dysmorphic facial features and hoarse voice. The mutation analysis was performed by whole exome sequencing. We found potentially pathogenic variant p.Lys430Glu in TRAF7 gene, de novo.

Conclusions: To our knowledge only about 50 patients with this syndrome were reported so far. The majority of pathogenic variants in TRAF7 were missense as in presented patient. CAFDADD syndrome should be taken under consideration in differential diagnosis of OHDO syndrome