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ABSTRACT BOOK

Marc Quinn 6 An other kiss (2006)

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Wednesday 18 of September

SESSION 1 – GENETIC DIAGNOSIS

15:15 - OBJECTIVE 3D PHENOTYPING UNCOVERS SUBCLINICAL FACIAL FEATURES IN A 3Q36 DELETION/KBG SYNDROME DUAL DIAGNOSIS

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Introduction: Co-existing Mendelian disorders can cause atypical phenotypes, challenging genetic diagnostics and clinical management. Deep familial phenotyping contributes to matching genomic and phenotypic data, but is particularly challenging for facial features. Here, we report an individual with a dual diagnosis of paternally inherited KBG syndrome and a maternally inherited 3q26 deletion. We performed three-dimensional (3D) facial phenotyping to investigate the presence of a subclinical dual phenotype.

Methods: We collected 3D facial photos of the index and his nuclear family, seven individuals with KBG syndrome and unaffected controls. We used dense surface registration to capture the facial shape and used craniofacial growth curves to assess facial features irrespective of age- and sex-related variation. We corrected the index's facial shape for the maternal (3q26del) and paternal (KBG) shape effects and performed principal component analysis and cosine-distance based analysis to objectively assess phenotypic similarity.

Results: Clinically, the index's facial gestalt is dominated by features associated with the 3q26 deletion. However, the cosine similarity to KBG syndrome is high, which is an objective indication of the presence of the KBG gestalt. Projecting the original phenotypes in a principal component space shows separate clustering of controls, KBG syndrome and both 3q26del carriers. After correcting the index for maternal shape effects, clustering reveals the corrected shape features the KBG gestalt.

Conclusion: We introduce objective 3D facial phenotyping to deconstruct facial features of major gene effects, unveiling subclinical facial features of KBG syndrome in an individual with a 3q26 deletion and KBG syndrome.

15:30 - GENETIC SYNDROMES AND IEMS AT A CROSSROADS: IF NOT MUCOPOLYSACCHARIDOSIS, WHAT IS IT?

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Introduction. Mucopolysaccharidoses, each one caused by loss-of-function variants in one among at least 13 different genes (10.3390/ijms25021113), are a group of recessive or X-linked inborn errors of metabolism sharing the pathomechanism of accumulation of undegraded glycosaminoglycans. Clinical presentation is commonly syndromic (10.3390/diagnostics10030172) and encompasses distinctive craniofacial gestalt. Disease course can be progressive when left untreated. A growing number of disease-modifying or curative time-sensitive therapies are available.

We hypothesized that the spectrum of genetic (and metabolic) syndromes clinically overlapping with mucopolysaccharidoses in the everyday practice of clinical genetics could be broader than usually reported in the medical literature.

Methods. Retrospective review of lab (Udine) and clinical (Udine and Trieste) charts of a consecutive case series based on referrals for total urinary GAGs testing.

Requests of total uGAGs (24-hour or spot) measured by DMB at our lab from 2015 to March 2022 were shortlisted after exclusion of the following records: unavailable clinical data; unclear final diagnosis; definite diagnosis of MPS or significantly elevated levels of uGAGs on two or more occasions; definite diagnosis of non-syndromic and non-genetic conditions.

Diagnostic labels and handles were extracted.

Results. We identified one case each of Cantú syndrome, Noonan syndrome, Myhre syndrome, Simpson-Golabi-Behmel syndrome, Xia-Gibbs syndrome, mucolipidosis IIIα/β, and alpha-mannosidosis.

Each case showed at least two clinical features in common with the 'mucopolysaccharidosis' category, supporting the indication for uGAG testing.

Conclusion. In our experience, even if limited in number, the differential diagnosis of mucopolysaccharidoses is wider than commonly thought and it includes conditions usually seen by syndromologists rather than experts in inherited metabolic disorders.

Therefore, we consider a reasonable diagnostic approach for clinical geneticists to arrange on-demand IEM consultations or, where available, to always have a low threshold for ordering affordable and low-complexity biochemical and molecular assays for treatable metabolic disorders that may be easily missed without targeted testing (e.g. uGAG or PCR for IDS gene inversion).

15:45 - GENETICS STUDY IN 23 CONGOLESE FAMILIES WITH UNEXPLAINED DEVELOPMENTAL DISORDERS IN THE FRAMEWORK OF THE DDD-AFRICA PROJECT

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Developmental Disorders (DD) affect about 1-3% of children globally. Genetic data related to DD in Central Africa are scarce. The aim is to increase our knowledge of the genetic aspects of DD in Central Africa, thus improving the diagnosis and guidance of affected individuals and their families. A total of 68 indexes were sequenced by WES as Trio (n=33), Duo (n=28), Extended Duo (n=2), Extended Trio (n=2) and Singleton (n=3) and interpreted for SNVs. A genetic diagnosis was reached in 23/68 indexes (34% of yield), with 21 different disorders. Two disorders were observed in 4 individuals (Noonan and Pheland McDermid syndromes). Two of those 23 indexes were diagnosed partially. Regarding the mode of inheritance, 19 indexes were diagnosed as AD, 8 of them *de novo*. Most of the families were diagnosed as duo (12/30), followed by Trio (10/35). For the Genotype-phenotype correlations, we explored the correlation between dysmorphism and diseases tool/literature, and the clinical aid by Face2Gene. Of 17/23 patients diagnosed with genetic syndromes and clinically assessed as dysmorphic, 10 presented a strong match with the phenotype reported in diseases database and literature. Five diagnostic criteria scores were found in the literature and all indexes presented with a score value corresponding to the score that could suggest the syndrome. In Face2gene, we found a mask for 7 diagnoses including KBG, Noonan, Stickler, Kabuki, Rett, Phelan-McDermid, Kaufman oculocerebrofacial syndromes. All patients ranked in top 10 diagnostic suggested by Face2Gene: KBG, Noonan and Stickler syndrome in 1st position, Kabuki syndrome in 2nd position, Rett syndrome in 3rd position, Phelan-Mcdermid in 7th position, and Kaufman oculocerebrofacial syndrome in 8th position.

Genotyping by exome analysis constitute a strong basis for genotype-phenotype correlation of DD in Central Africa. A yield of 34% was achieved based on the SNVs analysis. This is promising for the analysis of other types of variants.

Keywords: *Developmental disorders, Genetic study, Congolese, DDD-Africa*

16:00 - IS CLINICAL SYNDROMOLOGY STILL NEEDED IN THE ERA OF NEXT-GENERATION SEQUENCING? A RESPONSE FROM FIVE RECENT CLINICAL EXAMPLES

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Background/Objectives: The integration of high-throughput sequencing techniques into clinical genetics has led to a growing preference for a 'genotype-first approach'. This paradigm shift relegates the clinician to a more peripheral role, as the emphasis shifts towards prioritizing genetic information in the decision-making process. Despite these developments, the molecular basis of rare diseases, including neurodevelopmental disorders / intellectual disability remains elusive in roughly one-third to half of affected individuals. Even in

syndromes that are well characterized clinically and molecularly, it is not always possible to identify the underlying genetic cause.

Methods: We report on six patients from five families who had previously undergone multiple inconclusive molecular genetic analyses including (trio) whole exome sequencing. A meticulous clinical assessment, coupled with a targeted re-evaluation of genes associated with the resulting suspected conditions, could ultimately validate the molecular diagnosis in these individuals.

Results: We identified a homozygous splice site variant located next to consecutive thymine nucleotides which constitute a common artifact region in *VPS13B* in two brothers with Cohen syndrome; a maternal truncating variant in compound with a paternal single exon deletion in *VPS13B* in a boy with Cohen syndrome; a deletion of two exons in *TCF4* in a boy with Pitt-Hopkins syndrome, and a deletion of three exons in *KANSL1* in a patient with Koolen-de Vries syndrome. In another patient, the diagnosis of mosaic trisomy 16 was only discernible analyzing DNA extracted from uncultured fibroblasts.

Conclusion: These examples illustrate the pitfalls and challenges of next generation sequencing in routine diagnostics. They emphasize the critical nature of close collaborations between clinical and molecular geneticists as well as the important role of precise syndromological characterization to successfully unravel molecular causes, even in the age of modern high-throughput technologies.

16:15 EXPLORING UNCOMMON INHERITANCE PATTERNS: CLINICAL INSIGHTS INTO RARE GENETIC VARIANTS IN ESTABLISHED DISEASES WITH CASES

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Given the increasing utilization of whole-exome and whole-genome sequencing methodologies over the past few years, rare mechanisms underlying genetic diseases have started to emerge. With enhanced awareness among genetic professionals refining counseling and patient management, it becomes imperative to consider rare inheritance patterns for established diseases, especially when strong phenotypic indications are present. Consequently, we present four cases delineating unusual inheritance patterns for well-established diseases.

In Family 1, we observed, for the first time in the literature, a semi-dominant inheritance pattern in individuals carrying homozygous and heterozygous variants in the *LRP5* gene (OMIM*603506), leading to osteoporosis and short stature. Homozygous individuals had significantly more severe short stature and osteoporosis, as evidenced by lower Z-scores. Additionally, unlike previously reported cases with this variant, none of the individuals in the family exhibited ocular involvement.

In Family 2, two siblings with neurodevelopmental delay and epilepsy were found to harbor a homozygous variant in the *ASH1L* gene. While known pathogenic variants in this gene typically lead to 'Intellectual developmental disorder, autosomal dominant 52' (OMIM#617796) due to haploinsufficiency, no phenotypic manifestations were observed in the heterozygous parents in this family. Here, for the first time in the literature, we present the autosomal recessive form of the similar phenotype.

In Family 3, we present an unusual inheritance pattern of Marfan Syndrome (OMIM*134797), generally characterized by a 'dominant negative' effect in the *FBN1* gene, observed in two siblings. Interestingly, these

patients were found to harbor a homozygous variant in the *FBN1* gene. While individuals with Marfan Syndrome due to a 'loss-of-function' mechanism have been rarely reported in the literature, we report here a novel missense variant identified in these cases along with detailed clinical findings.

In Family 4, a case with dyskeratosis congenita carried a novel homozygous *TERC* (OMIM*602322) variant. Review of the literature revealed only one similar case with biallelic variants in the *TERC* gene, where the carrier mother had mild neutropenia. Based on these findings, the mechanism of action of the variant identified in the patient will be discussed in terms of semidominance or loss-of-function.

Annotating diseases and their associated inheritance patterns with genes can indeed pose challenges. Understanding the effects of genetic variants on transcripts and their interactions across phenotypic levels is crucial for accurate interpretation in medical genetics. Here, we emphasize the significance of discerning the functional consequences of genetic alterations, exemplified by the cases, to effectively classify novel variants in genetic analyses and accurately predict disease recurrence within families.

17:00 THE ERN ITHACA INTERNATIONAL CONSENSUS STATEMENT ON THE DIAGNOSIS AND MANAGEMENT IN RUBINSTEIN-TAYBI SYNDROME

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ERN ITHACA is the European Reference Network for Intellectual disability, TeleHealth, Autism and Congenital Anomalies. As a clinical research network, ERN ITHACA connects patient representatives and medical experts to develop best practices on diagnosis and management of rare developmental anomalies.

To fulfil its objectives, ERN ITHACA has supported the drafting of the consensus statement on the Rubinstein-Taybi Syndrome (RTS). Rubinstein-Taybi syndrome (RTS) is a multisystem disorder with physical, cognitive and behavioural characteristics, which can be caused by variants in two genes that regulate transcription via chromatin remodelling. Within the framework of the European Reference Network ITHACA a group of international experts recognised the importance of equal practices regarding diagnostic procedures and care for individuals with RTS.

From 20 January 2021 to 07 June 2022 the RTS consortium had several digital meetings to discuss the contents and the progress of the statement. Through 29 to 30 September 2022, the consortium met face-to-face in order to discuss the recommendations and to strengthen the collaboration around the syndrome. An anonymous digital voting process on the strength of the recommendations followed. 46 experts voted in total, and recommendations mainly obtained the grade A (general agreement allow full agreement with the recommendation). The manuscript has been published in open access at the Journal of Medical Genetics on March 2024.

A series of recommendations on clinical diagnostic criteria for RTS, molecular investigations, long-term management of various particular physical and behavioural issues, and care planning were outlined by the group of international experts and patient representatives.

The consensus statement is expected to contribute to improving the quality of care for RTS patients. ERN ITHACA provides methodological and logistic support to experts interested in writing a consensus statement on rare developmental syndromes. These consensus statements are equally requested from the patient representatives' community.

ERN ITHACA is financed by the EU4Health Programme, Grant Agreement nr. 101085231.

To cite the RTS Guideline: Lacombe, Didier et al. "Diagnosis and management in Rubinstein-Taybi syndrome: first international consensus statement." Journal of medical genetics, jmg-2023-109438. 12 Mar. 2024, doi:10.1136/jmg-2023-109438.

17:15 PHENOTYPIC SPECTRUM AND NATURAL HISTORY OF GILLESPIE SYNDROME

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Gillespie syndrome is a rare disorder caused by pathogenic variants in ITPR1 gene and characterized by the typical association of cerebellar ataxia and aniridia. Since its first description in 1965, less than 100 patients have been reported, only 30 with a molecular confirmation. ITPR1-associated ataxias are among the most common causes of genetic ataxia, both in children and adults, but the Gillespie phenotype is extremely rare, requiring specific dominant or biallelic alterations of ITPR1 to manifest.

We present two novel cases, carrying a loss-of-function variant in the Gly2539 residue: we describe their clinical evolution and discuss the updated phenotypic spectrum of the disorder with a thorough revision of all genetically-confirmed cases so far reported.

Data about development indicate that motor skills progressively improve over time and patients may reach some competences in late childhood: age range for sitting is 7-40 months, walking appears to be possible in most cases, although with assistance. Most patients present a delay in developmental milestones but intellectual disability is not invariably present: 17% have normal intelligence, 74% mild-to-moderate disability, and only 9% a severe impairment.

Neurological data about the patients from literature are poor, in most cases limited to the annotation of hypotonia and ataxia; in our cases, staggering and titubation persist over the years, as documented by the SARA score.

Cerebellar atrophy is present in all brain MRIs, predominantly affecting the vermis and sometimes associated with signal hyperintensity of diverse cerebellar structures; a follow-up MRI is available for 8 patients and demonstrated an atrophy progression in all cases but one.

General examination revealed normal growth in the majority of patients, with 5/12 having macrocephaly; facial dysmorphisms were present in 8 patients, scoliosis/kyphosis in 5, heart malformations in 4. Children with biallelic variants exhibit worse general conditions, with more recurrent presence of medical problems and/or malformative defects.

Molecular data indicate that Gillespie variants are sparse within the ITPR1 gene, with truncating variant located in the first three domains and less deleterious variants at the end of the third domain or in the last one; despite this, no clear genotype-phenotype correlation is found among patients carrying specific ITPR1 variants and patients sharing variants in the same amino acid residue show huge variability.

Overall clinical data suggest that Gillespie syndrome may be included in the group of the so-called Non Progressive Cerebellar Ataxias: observation of middle-aged patients and data about development indicate that motor skills often gradually improving over time, and that a discrete proportion of patients show no intellectual disability: these are key points both for clinicians and therapists providing care to Gillespie patients and for the families, particularly those with the younger patients.

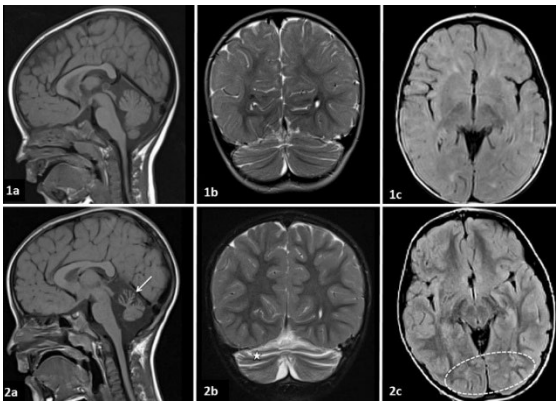

Figure 1. Brain MRI of Case 1: Panel 1 - Brain MRI at the age of 4 months: Sagittal TSE-T1w (1a) and coronal TSE-T2w (1b) showed no significant morphological abnormality, with asymptomatic small pineal cyst; axial T2w-FLAIR (1c) revealed a mild delay in deep white matter myelination. Panel 2 - Follow-up MRI at the age of 4 years: Sagittal TSE-T1w and coronal TSE-T2w showed marked cerebellar and vermis atrophy (2a, arrow) with folia prominence of the superior aspect of cerebellar hemispheres (2b, star). Residual altered signal intensity on T2w was still visible within deep white matter of occipital lobes (2c, dotted).

17:30 EXPANDING THE CLINICAL SPECTRUM OF SETD5-ASSOCIATED NEURODEVELOPMENTAL DISORDER

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Loss of function (LOF) variants of the *SETD5* gene are associated with an autosomal dominant developmental disorder, that fits within the category of mendelian disorders of the epigenetic machinery (MDEMs), a group of disorders that share common clinical features such as intellectual disability, developmental delay, growth retardation, skeletal anomalies, facial dysmorphisms. We here describe two patients with a *de novo* pathogenic variant of *SETD5* and unusual clinical features: a case with mild dysmorphisms and severe neurodevelopmental delay, and a patient presenting with Hirschprung's disease.

Our first patient is a three-year-old male, first-born of non-consanguineous Italian healthy parents.

At birth he presented with low weight, hypospadias and cryptorchidism. He showed feeding difficulties, mild dysmorphic features (anteverted nostrils, bulbous tip of the nose, long philtrum), trigonocephaly, prominent metopic ridge and synostosis of the metopic suture. At three years of age, the patient presented slow growth and a global neurodevelopmental delay, with scarce expressive language and a discrete comprehension of simple tasks, which was undermined by an extremely short attention span.

Due to the suspicion of a MDEM, whole exome sequencing (WES) was performed, identifying a *de novo* heterozygous variant of *SETD5*: c.1632_1633delGA (p.Glu544AspfsTer12).

Our second patient is a 4-year-old male, first-born of non-consanguineous Italian healthy parents and with no relevant family history, with the exception of a maternal cousin with megacolon.

The proband presented Hirschprung's disease, low weight, cryptorchidism and facial dysmorphisms, i.e., sunken nasal bridge, anteverted nostrils, large and distant central upper incisors and agenesia of upper lateral incisors, ears with underdeveloped upper helix and mild strabismus. He also presented with a developmental delay: he started walking at 24 months, started eating solid food at 4 years of age and had a speech impairment.

Due to the clinical presentation, WES was performed, allowing to identify a *SETD5 de novo* heterozygous LOF variant: c.1390C>T (p.Gln464Ter).

In conclusion, the cases described provide novel information about the variable phenotypic presentation of *SETD5*-associated disorder, especially expanding on the possible gastrointestinal involvement. In particular, while an association with Hirschprung's disease and KBG syndrome or other MDEMs had already been described, to the best of our knowledge, we here describe for the first time a patient with *SETD5*-associated disorder presenting with Hirshprung's diseases. We therefore suggest keeping this condition in mind when seeing a patient with neurodevelopmental delay and congenital megacolon.

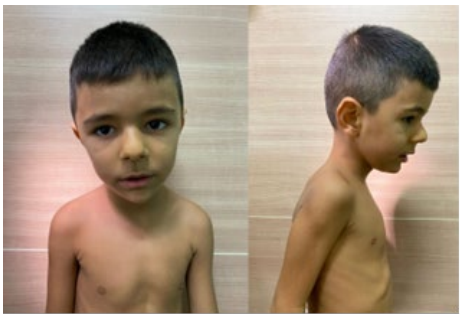

Figure 2: patient 2

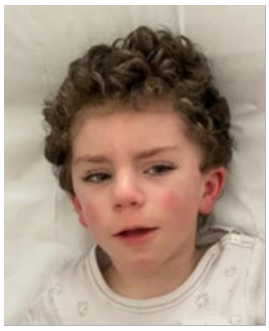

Figure 1: patient 1

17:45 SETD5-RELATAD NEURODEVELOPMENTAL DISORDER: 22 NOVEL INDIVIDUALS AND REVIEW OF THE LITERATURE

Berardo RINALDI[1], Beatrice CONTI[1], Elena DOMIZI[1], Alessandro DRAGHI[1], Giulietta SCUVERA[1], Claudia CESARETTI[1], Donatella MILANI[1], Federica NATACCI[1], Maria Francesca BEDESCHI[1] and the *SETD5* study group.

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Mendelian disorders of the epigenetic machinery are a broad group of neurodevelopmental disorders involving various components of the epigenetic machinery and other functionally related genes. *SETD5* gene (OMIM 615743) maps to chromosome 3 (3p25.3), and encodes for the lysine methyltransferase family member SET Domain Containing 5.

The primary role of SETD5 is promoting gene expression through the trimethylation of lysine 36 of histone H3 (H3K36), a crucial event for chromatin partitioning.

Pathogenic variants in *SETD5* are associated with a neurodevelopmental disorder known as "intellectual developmental disorder, autosomal dominant 23" (OMIM #615761, ORPHA: 404440) featuring intellectual disability of various degree, hypotonia, feeding difficulties, dysmorphic features, autism spectrum disorder, and behavioral disorders.

Up to know about 35 patients have been described in literature in several reports. We launched an international call via the ERN ITHACA website to improve the current knowledge of this condition and collected more than 20 novel cases.

We present our clinical data comparing them with what already known in literature.

18:00 CLINICAL DESCRIPTION, EXTENSIVE ASSESSMENT AND GENETIC ASPECTS OF A LARGE FRENCH COHORT OF MULLERIAN DUCT APLASIA/HYPOPLASIA IN THE FIELD OF UTERINE TRANSPLANTATION

Auriane COSPAIN[1,2], Ludivine DION[3,4], Sylvie ODENT[1], Erika LAUNAY[2], Laura MARY[2], Karine MORCEL[5], Daniel GUERRIER[6], Vincent LAVOUE[3,4], Sylvie JAILLARD[2,4]

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Introduction: Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome is the most severe form of Mullerian duct anomalies characterized by a congenital absence or severe hypoplasia of the uterus and of the upper two-thirds of the vagina, with normal functional ovaries. Mullerian duct dysplasia may be associated with other extra-genital abnormalities such as renal anomalies, skeletal anomalies, deafness or cardiac defects, corresponding to MURCS association (Mullerian duct aplasia, unilateral renal agenesis and cervicothoracic somite anomalies). The past two decades have witnessed significant advancements in MRKH research, particularly regarding genetic etiologies and fertility treatments such as human uterine transplantation.

As part of a multidisciplinary research endeavor at the Rennes Hospital Center (France) focusing on uterine transplantation in women with MRKH syndrome, we describe the genital and extra-genital phenotype of the initial French cohort of adults and fetus presenting with Mullerian duct dysplasia, and investigate patients' genetic profile.

Methods: The cohort of 110 individuals consists of 85 women with typical MRKH syndrome, 9 fetuses, and 16 individuals with Mullerian dysplasia spectrum anomalies. Extensive morphological evaluation followed the French guidelines, and the genetic analyses performed were karyotype, microarray, and whole exome sequencing.

Results: Among the 85 individuals with MRKH syndrome, 23.5% presented an isolated utero-vaginal aplasia after extensive evaluation, and 76.5% had associated malformations. We evidenced that 40% of the patients with MRKH diagnosis were under-assessed regarding associated malformations, suggesting an inadequate follow-up of these women. Interestingly, nearly 20% of patients tested had low AMH levels, indicating premature alteration of ovarian reserve.

In the complete cohort of Mullerian duct dysplasia spectrum anomalies of 110 individuals, karyotype analysis was carried out on 91 individuals, and found to be non-classical in 4 of them (including one woman with a 46,XY karyotype who was finally diagnosed with complete androgen insensitivity). Microarrays data were available for 74 individuals and revealed pathogenic micro-rearrangements in 6 individuals. Solo or trio exome sequencing was performed for 60 individuals and found out 6 pathogenic or likely pathogenic variants, 7 variants of uncertain signification, and 3 incidental data.

Conclusion: 40% of individuals with MRKH syndrome did not undergo a complete malformation assessment, highlighting the need for centralized management of these patients. In the field of Mullerian dysplasia

spectrum anomaly, this centralization allows genetic investigation that could lead to increase knowledge on MRKH syndrome. Recruitment is still ongoing in this cohort, and results are likely to vary substantially.

Thursday 19th of September

SESSION 3 – DEVELOPMENTAL ANOMALIES

09:00 INVITED TALK BY GUILLAUME CANAUD : OVERGROWTH SYNDROMES TREATMENT

09:45 PIK3CA-RELATED OVERGROWTH SYNDROME SPECTRUM IN LITHUANIAN COHORT

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Introduction: Overgrowth syndromes (OGs) are highly heterogeneous group characterized by generalized or segmental overgrowth. Some symptoms like large masses of tissue in different parts of the body and asymmetry between body parts are mostly found in segmental OGs. Increased neoplasia risk is a common concern for these patients.

Results: Here, we present 2 patients with lateralized OGs from Lithuanian OG study cohort. Main clinical features include asymmetric overgrowth in different parts of the body (truncal adipose overgrowth, hands, feet, legs). Both unrelated families have positive family history of cancer, including thyroid, kidney, lungs cancer and pheochromocytoma. The variant c.1798G>A; p. Glu600Lys in *PIKC3CA* was detected in a mosaic state in one of the patients. While an allele distribution of 50 % is expected for heterozygous variants, the sequencing data identified this variant in approximately 13 % of the NGS reads (16 of 123) of our patient. Therefore, approximately 26 % of the cells in the tested tissue (DNA extracted from blood) sample carry this variant. The detected mosaic variant is classified as likely pathogenic. Another patient revealed pathogenic variant c.1258T>C; p. Cys420Arg of *PIK3CA* gene in mosaic state which was detected in the tissue of large masses in the body after excision (16,24 %; ~ 32 % of the cells carry the variant in heterogeneous state).

Conclusions: It is difficult to estimate the risk for passing on a mosaic variant to potential offspring as that depends on the fraction (and type) of affected cells. Understanding molecular pathways involving *PIK3CA* is crucial for the follow-up of such patients. The patients are managed and treated following the current guidelines for *PIK3CA* – associated OGs.

Funding: The study is funded by the Research Council of Lithuania (No. S-LL-21-5).

10:00 THREE DOORS TO THREE GENES- MAPPING THE MOLECULAR DIAGNOSTIC JOURNEY OF A CLINICAL DIAGNOSIS

Tabib Dabir

DOORS is a rare autosomal recessive disorder characterized by Deafness, Onychodystrophy-Osteodystrophy, mental Retardation & Seizures. Campeau et al reported TBC1D24 as a causative gene in half of his patients in 2014. The group reported ATP6V1B2 variants in TBC1D24 negative cohort confirming its genetic heterogeneity. We report molecular diagnostic outcome of NI patients with clinical diagnosis of DOORS.

Case1 (2002): had additional features of hypotonia , facial dysmorphism and double outlet right ventricle. Zimmerman Laband (ZLS) was differential diagnosis. WES detected mutations in PIGN confirming the diagnosis of Multiple Congenital Anomalies Hypotonia Seizures syndrome (MCAHS).

Case2(2004): DDD identified KCNH1 mutation confirming the diagnosis of Temple-Baraitser syndrome (TBS).

Case3(1999):TBC1D24 was normal. Further research testing identified ATP6V1B2 variants.

DOORS has clinical overlap with DominatDeafnessOnychoDystophy syndrome (DDOD), (ZLS), TBS, Coffin Siris & glycosylphospotidylinositol deficiency disorders. ATP6V1B2 variants are reported in DDOD & ZLS . KCNH1 is implicated in TBS, ZLS & epilepsy. TBC1D24 causes AR deafness, epilepsy syndromes, AD deafness and DOORS syndrome. Mutations in PIGF, SMARCB1 have been reported in DOORS patients. However there is no consistent genotype phenotype correlation.

Our cases highlight the clinical overlap of these distinct clinical entities and their genetic heterogeneity. All patients had cardinal DOORS features and were diagnosed before the discovery of molecular etiology. None had TBC1D24 variants. WES confirmed two new diagnosis and ATP6V1B2 related DOORS in the third. The cases highlight the contribution of gene agnostic approach by WES in diagnosis by distinguishing these syndromes at molecular level raising the issue of (splitting the phenotype vs lumping the syndromes. Myopathic face and hypotonia were distinguishing features consistent with molecular diagnosis in case 1 & 2 respectively. Shared pathway and protein –protein interactions may explain the overlapping clinical phenotypes. It is perhaps prudent to define syndromes as a gene specific related disorders rather than the phenotype based description.

10:15 DOMINANTLY ACTING VARIANTS IN VACUOLAR ATPASE SUBUNITS IMPAIR LYSOSOMAL FUNCTION CAUSING A MULTISYSTEMIC DISORDER WITH NEUROCOGNITIVE IMPAIRMENT AND MULTIPLE CONGENITAL ANOMALIES

Francesca Clementina RADIO[1,#], Giovanna CARPENTIERI[1,2,#], Serena CECCHETTI[3], Gianfranco BOCCHINFUSO[4], Chiara LEONI[5], Roberta ONESIMO[5], Paolo CALLIGARI[4], Agostina PIETRANTONI[6], Andrea CIOLFI[1], Marco FERILLI[1], Cristina CALDERAN[7], Gerarda CAPPUCCIO[8], Simone MARTINELLI[2], Elena MESSINA[1], Viviana CAPUTO[9], Ulrike HÜFFMEIER[10], Cyril MIGNOT[11], Stéphane AUVIN[12], Yline CAPRI[13], Charles Marques LOURENCO[14], Bianca E. RUSSELL[15], Ahna NEUSTAD[15], Nicola BRUNETTI PIERRI[8,16,17], Boris KEREN[11], André REIS[10], Julie S. COHEN[18,19], Alexis HEIDLEBAUGH[18], Clay SMITH[18,19], Christian T. THIEL[20], Leonardo SALVIATI[7], Giuseppe ZAMPINO[5], Philippe M. CAMPEAU[21], Lorenzo STELLA[4], Elisabetta FLEX[2,22,*] , Marco TARTAGLIA[1,22,*]

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The vacuolar H^+-ATPase (V-ATPase) is a functionally conserved multimeric complex localized at the membranes of many organelles where its proton-pumping action is required for proper lumen acidification. The V-ATPase complex is composed of several subunits, some of which have been linked to human disease. Dominantly acting variants in *ATP6V1B2* are associated with a wide clinical spectrum, including dominant deafness–onychodystrophy syndrome (DDOD [MIM 124480]), deafness–onychodystrophy–osteodystrophy–mental retardation–seizures syndrome (DOORS [MIM 220500]), and Zimmermann-Laband syndrome (ZLS [MIM: PS135500]). Patients with DDOD usually show normal development and cognitive function, while individuals with DOORS and ZLS present with intellectual disability (ID), with or without seizures. These disorders share hypoplasia/aplasia of nails and terminal phalanges, while a recognizable craniofacial appearance, gingival overgrowth, and hypertrichosis also characterize ZLS. A recurrent truncating variant in *ATP6V1B2* has been reported in both DDOD and DOORS, suggesting that these conditions are within a spectrum of a single disorder caused by altered V-ATPase function. No clinical phenotype has been reported to be caused by altered function of *ATP6V1C1*, to date.

We causally link a *de novo* missense variant in *ATP6V1C1* to a neurodevelopmental phenotype with features resembling DOORS, and more accurately define the clinical spectrum of dominantly acting *ATP6V1B2* variants. We also provide evidence that the identified amino acid substitutions result in a gain-of-function mechanism upregulating V-ATPase function driving increased lysosomal acidification. We demonstrate a disruptive effect of these variants on lysosomal morphology, localization and function, resulting in a

defective autophagic flux and accumulation of lysosomal substrates. The clinical features observed in the subject with the *ATP6V1C1* variant show a substantial overlap with DOORS, further supporting the occurrence of a phenotypic continuum characterizing DOORS, DDOD and ZLS. Notwithstanding the relatively small number of affected individuals with *ATP6V1B2* variants reported thus far, first genotype-phenotype correlations are emerging. Among these, the mutation cluster affecting residues located close to the ADP/ATP binding site share cognitive and motor functions impairment, ID, seizures and distinctive facial features.

In conclusion, we show a continuum in the clinical spectrum associated with dominant variants affecting the *ATP6V1C1* and *ATP6V1B2* subunits causing upregulation of the V-ATPase function. Notwithstanding the multiple processes that are altered in cells expressing these variants, increased lysosomal acidification appears the driver event of such pleiotropy, indicating that these disorders can be considered as lysosomal diseases. These findings provide a rationale for the use of molecules targeting the upregulated V-ATPase function to ameliorate evolutive features in these subjects.

SESSION 4 - PRENATAL CASES & SYNDROME DELINEATION

11:00 INVITED TALK BY NATALIYA DIDONATO: BRAIN MALFORMATIONS

11:45 TWO UNRELATED CASES OF PRENATAL SHWACHMAN-DIAMOND SYNDROME: A DIAGNOSIS COMPLICATED BY A RARE CLINICAL PRESENTATION AND A PSEUDOGENE

Vanden Eynde N[1], Slegers I[1], Vantroys E[1], Symoens S[2], Doné E [3], Leus A [4], Brock S[5], Keymolen K[1], Hes FJ[1], Dimitrov B[1] and van Berkel K[1]

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Shwachman-Diamond syndrome (SDS) is a rare autosomal recessive disorder characterized by a triad of bone marrow dysfunction, skeletal abnormalities, and exocrine pancreatic dysfunction. The most common features in affected children are failure to thrive, short stature, and neutropenia resulting in recurrent infections. SDS poses several diagnostic challenges, especially during fetal life. First, not all features are seen during pregnancy, e.g. pancreatic dysfunction. As a result, prenatal and postnatal phenotypes may be different, and prenatal reports are scarce. Second, if patients present with severe skeletal features (a bell-shaped or long narrow thorax) during fetal life, the first suspected diagnosis is asphyxiating thoracic dystrophy (e.g. Jeune syndrome). Third, the molecular diagnosis is made by diagnosing biallelic loss-of-function pathogenic variants in the SBDS gene but molecular genetic analysis is hampered by the presence of a pseudogene (SBDSP1). These two genes are located in proximity on chromosome 7, and both mismapping and conversion events between the 2 loci resulting in a true mutation have been described.

We report two unrelated prenatal cases of SDS, presenting as a rare clinical presentation of asphyxiating thoracic dystrophy, where initial clinical molecular testing did not reveal the diagnosis. Further molecular testing after a multidisciplinary reassessment was able to reveal the diagnosis of SDS by germline pathogenic SBDS variants (c.258+2T>C p.(?) and c.184A>T p.Lys62Ter).

12:00 PRENATAL CLINICAL FINDINGS IN RAUCH-STEINDL SYNDROME: WIDE MALFORMATIVE PHENOTYPIC SPECTRUM OR DUAL DIAGNOSIS?

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Background: Missense or loss-of-function mutations involving *NSD2* gene are related to autosomal dominant Rauch-Steindl Syndrome (RAUST; MIM 619695). Interstitial duplications (usually ~1.6 Mb) in the 3q29 region are associated to a microduplication syndrome (MIM 611936) with incomplete penetrance and highly variable expressiveness. Both conditions present with neurodevelopmental involvement and facial dysmorphisms; major malformations have been less frequently described. Here we present a prenatal clinical case characterized by polymalformative features. Genetic assessment was performed on fetal DNA extracted from amniocytes, whose results raised the doubt of a dual diagnosis.

Case description: A couple came to our attention during their first pregnancy, resulted in TToP following the fetal ultrasound detection of IUGR, microcephaly, cerebellar hypoplasia, lateral cerebral ventriculomegaly with irregular ventricle contour, unidentifiable septum pellucidum, aberrant right subclavian artery, bilateral clubfoot, micrognathia. CGH-array analysis revealed the presence of a 3q29 paternal duplication (425-595 kb; chr3:196.892.527-197.317.103) involving 5 genes, including *DLG1* and *BDH1*. Since the uncertain significance of the duplication, we proceeded with trio WES analysis, which revealed the presence of the *de novo* pathogenic heterozygous variant c.1676_1679del p.(Arg559Thrfs*38) in *NSD2,* allowing the diagnosis of Rauch-Steindl Syndrome in the fetus.

Discussion: Overall, the fetal ultrasound features appear partially compatible with both the described conditions. Despite this, IUGR and cephalic biometry appear particularly overlapping with what reported in individuals affected by RAUST; furthermore, the clinical significance of small duplications involving the 3q29 region has yet to be fully elucidated. On the other hand, ventricular/cerebellar involvement and clubfeet would seem more consistent with microduplications involving the 3q29 region. Therefore, in the current state of knowledge it is not possible to exclude a synergistic effect of the two alterations in determining the phenotype. Either way, our experience shows that in presence of 3q29 small duplications and major malformations, it should be recommended pursuing with more extensive diagnostic investigations, as in our case WES analysis allowed a diagnosis of Reich-Steindl Syndrome to be made, enabling to provide the parents with accurate prenatal counselling for future pregnancies.

12:15 GENOMIC FINDINGS IN NON-IMMUNE HYDROPS FETALIS AFFILIATION : INSTITUTE OF HISTOLOGY AND EMBRYOLOGY, UNIVERSITY OF LJUBLJANA, SLOVENIA

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Non-immune hydrops fetalis (NIHF) is a condition that occurs in 1 in 1700 to 3000 pregnancies and is often fatal. It has numerous genetic causes, including chromosomal and monogenic disorders. Clinical diagnosis remains challenging. The aetiology remains unexplained in about 60-70% of cases, although more than 130 genes have been associated with NIHF.

We performed a retrospective analysis of the institutional congenital anomalies registry presenting with non-immune foetal hydrops or cystic hygroma or increased nuchal translucency (NT ≥ 3.5 mm). We identified 39 patients who had a previous non-diagnostic karyotype or chromosomal microarray analysis. Both cases with isolated NIHF and cases with NIHF associated with multiple congenital anomalies were included in this study. We excluded cases in which a non-genetic cause for the hydrops was established (congenital viral infection, alloimmunisation or twin-twin transfusion syndrome).

We identified diagnostic genetic variants in 20.5% of cases and variants of uncertain significance in a further 20.5% of cases. Disease categories included disorders affecting the RAS-MAPK cell signalling pathway - RASopathies (37.5 %), neurodevelopmental disorders (25 %), musculoskeletal disorders (25 %), and inborn errors of metabolism (12.5 %).

In a case series of 39 foetuses with unexplained NIHF, we identified a diagnostic genetic variant in 20.5% of cases. As previously reported, RASopathies were the most common group of disorders. Determining the genetic aetiology of NIHF in the prenatal period is crucial as it informs decisions on pregnancy management, anticipation of neonatal care needs, provision of timely treatments and counselling of families on prognosis and risk of recurrence.

12:30 LOSS OF PHOSPHOLIPASE PLAAT3 CAUSES A MIXED LIPODYSTROPHY AND NEUROLOGICAL SYNDROME DUE TO IMPAIRED PPARγ SIGNALING3

Nika Schuermans[1,2,32]*, Salima El Chehadeh[3,4,5,32]*, Dimitri Hemelsoet[6,32]*, Jérémie Gautheron[7,32]*, Marie-Christine Vantyghem[8,9], Sonia Nouioua[10,11], Ferroudja Ramdane Cherif[10,11], Meriem Tazir[11,12], Corinne Vigouroux[7,13], Martine Auclair[7,13], Elke Bogaert[1,2], Sara Dufour[2,14,15], Fumiya Okawa[16], Pascale Hilbert[17], Nike Van Doninck[18], Marie-Caroline Taquet[19], Toon Rosseel[1], Griet De Clercq[1,2], Elke Debackere[1,2], Paul J. Coucke[1,2], Carole Van Haverbeke[20], Jo Van Dorpe[20], Jon Andoni Urtizberea[21], Jean-Baptiste Chanson[22], Benoit Funalot[23,24], François-Jérôme Authier[24,25], Sabine Kaya[26], Wim Terryn[27], Steven Callens[28], Bernard Depypere[29], Bruce Poppe[1,2], Francis Impens[2,14,15], Noboru Mizushima[16], Arnaud V. Vanlander[30], Patrick Verloo[30], Christel Depienne[4,26], Isabelle Jéru[7,31,33] & Bart Dermaut[1,2,33].

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Background/Objectives: Phospholipase A/acyltransferase 3 (PLAAT3) is a phospholipid-modifying enzyme predominantly expressed in neural and white adipose tissue (WAT). It is a potential drug target for metabolic syndrome, as Plaat3 deficiency in mice protects against diet-induced obesity. We identified seven patients from four unrelated consanguineous families, with homozygous loss-of-function variants in *PLAAT3*, who presented with a lipodystrophy syndrome with loss of fat varying from partial to generalized, muscular

hypertrophy and chronic muscle pain, associated with metabolic complications, as well as variable neurological features including demyelinating neuropathy and intellectual disability. We aimed to clarify the pathogenic mechanism of PLAAT3-related lipodystrophy syndrome and to further address the role of PLAAT3 in human adipogenesis.

Methods: We performed multi-omics analyses of mouse Plaat3−/− and patient-derived WAT. We next performed CRISPR-Cas9-mediated PLAAT3 inactivation in human adipose stem cells and assessed the adipocyte differentiation signaling using morphological and expression studies.

Results: Multi-omics analysis of mouse Plaat3−/− and patient-derived WAT showed enrichment of arachidonic acid-containing membrane phospholipids and a strong decrease in the signaling of peroxisome proliferator-activated receptor gamma (PPARγ), the master regulator of adipocyte differentiation. Accordingly, CRISPR-Cas9-mediated PLAAT3 inactivation in human adipose stem cells induced insulin resistance, altered adipocyte differentiation with decreased lipid droplet formation and reduced the expression of adipogenic and mature adipocyte markers, including PPARγ.

Conclusion: These findings establish PLAAT3 deficiency as a hereditary lipodystrophy syndrome with neurological manifestations, caused by a PPARγ-dependent defect in WAT differentiation and function. The role of PLAAT3 in patients' neurological phenotype remains to be established.

12:45 TWO FEMALE PATIENTS DIAGNOSED WITH ZC4H2-ASSOCIATED RARE DISORDERS

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ZC4H2-Associated Rare Disorders (ZARD) include Wieacker-Wolff syndrome (WRWF) and Wieacker-Wolff syndrome, female-restricted (WRWFFR) phenotypes that are rare, severe, X-linked neurodevelopmental disorders. WRWFFR is X-linked dominant syndromic form that affects females. WRWF affects mostly male patients with X-linked recessive inheritance, while females may manifest mild features. Approximately 100 patients have been reported in the literature so far. Clinical features are characterized by fetal akinesia causing arthrogryposis multiplex congenita at birth, hypotonia, oculomotor apraxia, facial and bulbar weakness, skeletal abnormalities such as scoliosis and foot deformities, global developmental delay and intellectual disability. Dysmorphic facial features include hypotonic facies, ptosis, microretrognathia, and small mouth.

Our first patient was a 12-year-old female who was referred to our outpatient clinics for evaluation for arthrogryposis congenita multiplex and neurodevelopmental delay (NDD). Around age of 6 she had developed myoclonic seizures. At her EMG she had motor neuropathy with anterior horn involvement. She did not have head and neck control or could not use any words. At her physical examination, all anthropometric measurements were below 3rd percentile. She had deep-set eyes, downslanting palpebral fissures, and a prominent nasal bridge. She had flexion contracture and ulnar deviation of right radiocarpal joint, extension contracture of interphalangeal and metacarpophalangeal joints of second finger of the left hand, flexion contracture of metacarpophalangeal joint of the 3rd finger of left hand, flexion contractures of 4th and 5th finger interphalangeal and metacarpophalangeal joints of the left hand. She had pes equinavarus deformity at the right foot and pes cavovarus deformity with hallux valgus at left foot. Whole exome

sequencing was performed and a novel, de novo, pathogenic *ZC4H2*(NM_018684.4):c.412C>T (p.Gln138Ter) variant was detected in a heterozygous state.

The second patient was a 6-year-old female who was referred to our outpatient clinics for evaluation for NDD and skeletal abnormalities. She was diagnosed with bilateral pes equinovarus deformities and developmental dysplasia of the left hip at birth. She could not talk or walk without support. Her anthropometric measurements were in normal range. She had bilateral epicanthus, short palpebral fissures, short neck, bilateral hypoplasia of the index fingers, bilateral hockey lines, and bilateral brachydactyly of the great toes. Whole exome sequencing was performed and a pathogenic *ZC4H2*(NM_018684.4):c.199C>T p.(Arg67Ter) variant was detected in a heterozygous state.

Here we report two female patients, one harboring a novel variant, diagnosed with ZARD with variable clinical features. We believe this report will expand our understanding of this rare phenotype.

SESSION 5 – ACRONYM SYNDROMS

14:55 10TH CASE OF NEDMAGA SYNDROME IN A 22-YEAR-OLD GIRL WITH COMPLEX NEURODEVELOPMENTAL DISORDER AND CRANIOFACIAL DYSMORPHISM

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The key role of the ZSWIM6 (Zinc finger swim domain-containing protein 6) gene in neuronal development and function has recently been delineated. Two different variants in ZSWIM6 are known to be associated with two distinctive rare autosomal dominant neurodevelopmental disorders: Neurodevelopmental disorder with movement abnormalities, abnormal gait, and autistic features (NEDMAGA, MIM617865) and Acromelic frontonasal dysostosis (ADNF, MIM603671).

The NEDMAGA is caused by a recurrent de novo nonsense ZSWIM6 variant p.(Arg913Ter) (NM_020928.1). The variant transcript may escape NMD and produce a protein lacking the Sin3-like domain, and the truncated protein may cause a dominant-negative effect. NEDMAGA is characterized by delayed psychomotor development (DD), severe to profound intellectual disability (ID), delayed walking with broad-based and unsteady gait, autism and absence of meaningful language. ZSWIM6 was associated with NEDMAGA in 2017, and since then only nine patients have been reported.

We present a currently 22-year-old girl coming from the first pregnancy of unrelated Caucasian parents, complicated by the twin loss in the first trimester and finding of a mass on the fetal calf. Subsequent examinations (magnetic resonance imaging, karyotyping) revealed normal results. Developmental regression with deepening of autistic features in behaviour was evident around the age of two. Later on she presented with delayed psychomotor development, severe intellectual disability, autistic spectrum disorder, obesity, hip dysplasia, microcephaly, strabismus, and dysmorphic facial features (broad face, arched

eyebrows, deep-set eyes, sunken root of the nose, deep philtrum, large mouth with narrow upper lip, Cupid's bow, small, low-set ears and large tongue). The girl is nonverbal with limited comprehension. She has happy disposition with bursts of laughter, hyperactivity and pica. Her gait is unsteady and wide-based. She has spastic quadriparesis and numerous movement stereotypes.

The proband was examined sequentially and was also included in several international projects, but the results did not lead to clarification of her diagnosis, until finally trio exome sequencing revealed the recurrent de novo nonsense ZSWIM6 variant p.(Arg913Ter) previously reported in the nine NEDMAGA patients.

Our patient confirms the typical spectrum of symptoms of NEDMAGA. Based on milder neurodevelopmental phenotypes observed in a very limited number of patients with ZSWIM6 deletions, haploinsufficiency does not appear to be the causative disease mechanism of NEDMAGA. The disorder may belong to several human diseases caused by C-terminal protein-truncating mutations. The exact molecular and cellular mechanism explaining how the two ZSWIM6 variants cause distinct phenotypes remains to be determined.

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15:05 NEW CASE OF MEDNIK SYNDROME: FEEDING RELATED NON-MOTOR SEIZURES COULD BE A NEW FEATURE?

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MEDNIK Syndrome (MS) is a neurocutaneous disease associated with biallelic variants of the *AP1S1* gene. The involvement is multisystemic and includes ichthyosis, intellectual disability, deafness, peripheral neuropathy and a severe enteropathy often resulting in neonatal mortality. To date, only 14 cases have been reported in literature. We present the clinical course of a newborn girl with MS and a review of the literature.

A girl, third child of consanguineous parents, born at term, presented since birth congenital non-infectious diarrhoea. At 15 days of age, breastfeeding was ceased and total parenteral nutrition (TPN) was introduced. At 23 days of age, re-feeding was attempted but failed due to recrudescence of enteropathy and simultaneous onset of focal epileptic non-motor seizures, which resolved upon reinstating TPN. At 4 months of age, she was weaned of TPN and from 6 months onwards, she remained seizure free with anti-epileptic therapy and zinc-acetate supplementation. Additionally, she presented with ichthyosis, mild hearing loss and

hyporigenerative anaemia. At 2 years of age she showed axial hypotonia, psychomotor delay and growth retardation.

SNP Array analysis revealed multiple regions of homozygosity. Subsequent clinical exome analysis identified the homozygous c.256C>T p.(Arg86Ter) variant in the *AP1S1* gene, resulting in a premature stop codon confirming the diagnosis.

Given the rarity of the condition, the high neonatal mortality and the limited therapeutic options available, we present this case along with a review of the literature, outlining the main clinical and molecular aspects of the disease including electrophysiological features never reported before.

15:15 EXPLORING CLINICAL VARIABILITY OF STAR SYNDROME: A CASE REPORT OF AFFECTED MONOZYGOTIC TWINS

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STAR (toe **S**yndactyly, **T**elecanthus and **A**nogenital and **R**enal malformations) syndrome is an ultrarare, X-linked dominant disorder caused by a genetic variant in or involving *CCNQ* gene (formerly known as *FAM58A*). To our knowledge, only 17 patients with this condition have been described in literature.

We present MC/DA twins born from 2nd pregnancy and 1st delivery to unrelated parents. 1st pregnancy was terminated due to early intrauterine growth restriction and Patau syndrome diagnosis by NIPT. During current pregnancy circulation defect in *a. cerebri media* of 2nd twin was observed. Birth was induced at 34 gestational weeks as intrauterine growth restriction of both fetuses was suspected. 1st twin's (female) birth weight was 1956 g, length – 44 cm, head circumference – 32 cm, Apgar score – 8/9. She presented with anal atresia, suspected perineal fistula and mild syndactyly of III-IV-V toes. Clinical screening discovered no anomalies of internal organs. 2nd twin's (female) birth weight was 1560 g, length – 41 cm, head circumference – 31 cm, Apgar score – 7/8. Her phenotype was similar, but significantly more severe with low-set, dysplastic earlobes, suspected *aplasia cutis* of hairy scalp area, pronounced *talipes equinovarus* deformity of feet, symmetric syndactyly of III-IV-V toes, hypoplastic labia, anal atresia with suspected rectovaginal fistula, skin defect of the sacral region. Clinical investigations also showed choroid cysts of the left lateral brain ventricle, small ventricular and 2nd degree atrial septal defects of the heart, hypoplastic right kidney, Th12 and L3 vertebral dysplasia, congenital hip dislocation, congenital deformity of sacrum and coccyx.

Karyotype analysis was normal. SNP-CGH assay of 2nd twin was performed and 38 kb deletion in Xq28 locus was detected, encompassing *ATP2B3, BGN, CCNQ* genes. Segregation analysis in other family members is currently underway.

15:25 NAVIGATING THE OVERLAP: GENETIC INSIGHTS INTO CDLS-LIKE PHENOTYPES LEADING TO A CHOPS SYNDROME DIAGNOSIS

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Background: Distinguishing Cornelia de Lange Syndrome (CdLS) from other chromatinopathies such as CHOPS syndrome is complex due to overlapping clinical features. This case emphasizes the importance of extensive genetic analysis in cases presenting with CdLS-like phenotypes but where other clinical details may suggest alternative diagnoses.

Case Presentation: A 9.5-month-old male, initially presented with laryngomalacia, hypotonia, and hearing impairments. By three months, the patient was unable to hold his head up. Physical examination revealed microcephaly, brachycephaly, a short forehead, arched eyebrows with synophrys, a wide palpebral fissure, long eyelashes, a beaked nose, a long philtrum, thin upper vermilion, low-set large ears, retrognathia, brachydactylic fusiform fingers, and an umbilical hernia. His growth metrics at referral were significantly below average: weight of 7.2 kg (-2.08 SD), height of 64 cm (-3.25 SD), and head circumference of 40 cm (-4.1 SD). These clinical features initially suggested a diagnosis of CdLS.

Genetic Analysis and Diagnosis: Despite the suggestive clinical presentation of CdLS, whole exome sequencing (WES) was performed, identifying a rare missense variant AFF4 (NM_014423.4) c.772C>G (p.Arg258Gly). This finding confirmed a diagnosis of CHOPS syndrome, thus refining the clinical management and genetic counseling for the family. Subsequent referral to pediatric cardiology revealed ventricular septal defect (VSD), atrial septal defect (ASD), and pulmonary hypertension (PH). The patient underwent successful surgical intervention to address these cardiac issues.

Conclusion: This case underlines the necessity for broad genetic testing such as WES in patients presenting with CdLS-like manifestations. Identifying a specific mutation in the AFF4 gene, typical for CHOPS syndrome, highlights the essential role of genetic diagnostics in accurate disease identification and management. The discovery of significant cardiac anomalies further emphasizes the importance of comprehensive post-diagnostic evaluations and multidisciplinary management in chromatinopathies.

Keywords: Chromatinopathies, Cornelia de Lange Syndrome, CHOPS syndrome, AFF4 mutation, differential diagnosis, whole exome sequencing, genetic analysis, pediatric cardiology.

15:35 UNUSUAL PRESENTATION OF COFS: NEONATAL CHOLESTASIS AND ABSENCE OF ARTHROGRYPOSIS

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ERCC5 is a component of the nucleotide excision repair machinery. Biallelic *ERCC5* mutations have been associated with a spectrum of phenotypes ranging from Xeroderma pigmentosum to Cockayne syndrome and the more severe early onset cerebrooculofacioskeletal syndrome (COFS). This case presents a patient with COFS in the absence of arthrogryposis and with neonatal cholestasis. A female infant is the first child of

non-consanguineous parents. She was delivered prematurely at 36+1 weeks gestation. Prenatal ultrasound findings included IUGR, bilateral ventriculomegaly, mild tricuspid-mitral regurgitation, cardiomegaly. On examination, bitemporally narrow, hypertrichosis on the forehead, short palpebral fissures, prominent nasal root, low and retroverted ears and mild micrognathia were noted. She also had bilateral microphthalmia, congenital cataracts, mild 5th clinodactyly on the right and bilateral plantar line. There were no arthrogryposis signs and no skeletal anomalies noted.

Following delivery, she was closely monitored due to respiratory distress. She had epileptic seizures with evidence of epileptic activity on EEG. Brain MRI revealed a hypoplasia of brainstem and cerebellar hemispheres, enlarged cisterna magna and delayed white matter myelination. She had severe gastro-oesophageal reflux.

Laboratory examination demonstrated an elevated level of liver function tests. Abdominal ultrasonography findings supported cholestasis.

CGH-array was unremarkable. Clinical exome sequencing analysis of the propand revealed compound heterozygous variants, c.204del p.(Arg69GlufsTer15) and c.412C>T p.(Arg138Ter), in the *ERCC5* gene (NM_000123.4). The variants were classified as pathogenic according to ACMG criteria. The panel result was confirmed by subsequent whole-genome sequencing. The patient diagnosed with COFS died of respiratory failure at the age of 2 months.

In this case, we presented a patient with COFS, a rare autosomal recessive disorder associated with biallelic mutations in the *ERCC5* gene. Despite the absence of typical arthrogryposis or skeletal anomalies, the patient exhibited characteristic features of COFS, including microcephaly, congenital cataracts, facial dysmorphism, and neurological abnormalities furthermore; the presence of neonatal cholestasis adds to the clinical complexity of the case. While cholestasis is not a typical feature, it underscores the multisystemic involvement of COFS and highlights the importance of comprehensive clinical evaluation in these patients.

In conclusion, our case expands the phenotypic spectrum of *ERCC5*-related disorders by presenting a rare manifestation of COFS without arthrogryposis. These findings highlight the complexity and variability of *ERCC5*-related disorders.

15:45 3M SYNDROME: FROM PHENOTYPE TO GENOTYPE. A SOLVED COMPLEX CASE

Isabelle Bacchi[1,2], Emanuele Coccia[1,2], Gianluca Contrò[1], Stefano Giuseppe Caraffi[1], Marzia Pollazzon[1], Chiara Sartori[3], Roberta Zuntini[1], Rachele Teneggi[1], Maria Chiara Baroni[1,2], Adelaide Peruzzi[1,2], Irene Ambrosetti[1,2], Ekkehard Lausch[4], Uta Matysiak[5,6], Valeria Orlando[7], Antonio Novelli[7], Andrea Superti-Furga[8,9], Livia Garavelli[1]

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Background/Objectives: Three M (3M) syndrome is an autosomal recessive disease characterized by short stature, facial dysmorphism and skeletal anomalies. Deleterious changes in the *CUL7*, *OBSL1* and *CCDC8* genes establish the diagnosis. We describe the clinical evolution of a 12-year-old Italian boy who showed significant growth retardation and characteristic facies. Functional study of a *CUL7* variant that presumably affects splicing supports our clinical diagnosis.

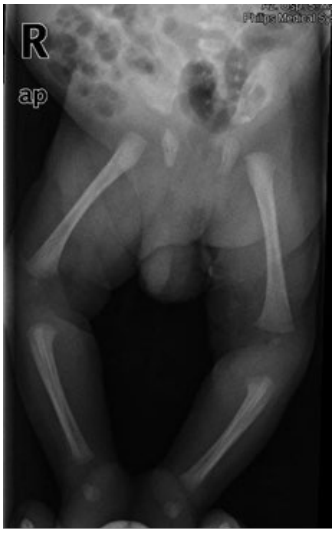
Methods: We conducted direct sequencing analysis of selected genes and then NGS panel for skeletal dysplasias. Transcript analysis using RNA extracted from fresh blood samples was performed by RT-PCR.

Results: At 6 months our patient showed a phenotype strongly suspicious for 3M syndrome. He had relative macrocephaly, dolichocephaly, frontal bossing, hypoplastic midface, fleshy nasal tip, long philtrum, pointed chin, short and broad neck with prominent trapezium, pectus excavatum, short, wide and flared thorax, transverse grooves on anterior chest, square shoulders with winged scapulae, enlarged abdomen, short limbs, prominent heels, hypotonia, joint laxity. Furthermore, radiographic images showed thin long bones, diaphyseal constriction and cortical thickening, high vertebrae. Around age 2, a subsequent evaluation revealed the same main clinical features with hyperlordosis.

Direct sequencing of *CUL7, OBSL1* and *CCDC8* genes was carried out: the analysis identified a paternal, heterozygous variant c.2063+5G>C in *CUL7* and a maternal, heterozygous variant c.487_489delAAG in *OBSL1,* both classified as VUS. The parents decided not to continue the investigations, however they returned after 10 years in relation to poor growth. An NGS panel for skeletal dysplasias was then performed: a maternal likely pathogenic variant c.4391A>C (p.His1464Pro) in the *CUL7* gene was identified, along with the previously reported c.2063+5G>C *CUL7* variant. Transcript analysis showed that the paternal *CUL7* variant is responsible for exon 8 skipping, which altered the open reading frame.

Conclusions: Our report highlights that patient phenotyping can quicken the diagnostic process: functional analysis demonstrated an effect on splicing, which, together with the characteristic clinical and radiological features, supports the pathogenicity of the c.2063+5G>C variant in *CUL7*.

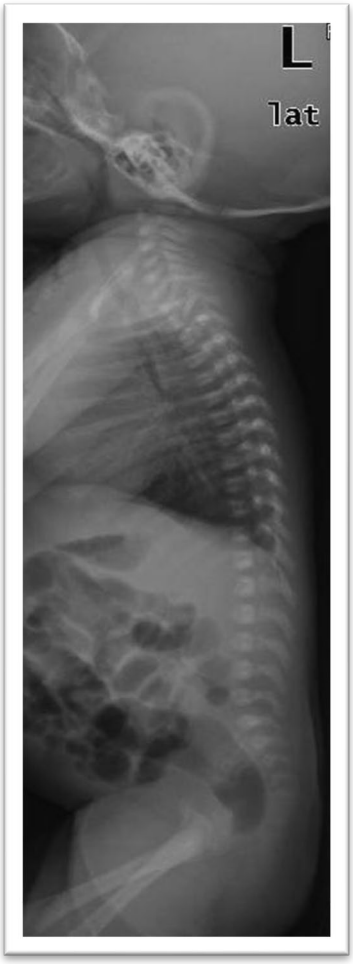
Index patient: c.[*CUL7*:2063+5G>C];[*OBSL1*:487_489delAAG]
Father: c.[*CUL7*:2063+5G>C];[=]
Mother: c.[*OBSL1*:487_489delAAG];[=]

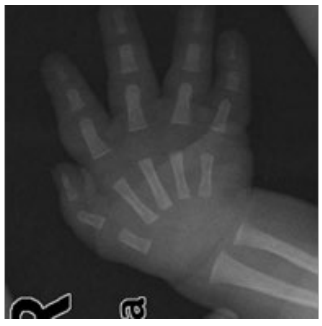


Age: 6 months

- Length: 58 cm (<<3° p)
- Weight: 5.250 Kg (<<3° p)
- HC: 43.5 cm (25°-50°p)
- Genetic target: 178.5 cm

Hypoplastic midface, fleshy nasal tip, long philtrum, pointed chin, short thorax, prominent abdomen





Thin bones
Diaphyseal constriction
Cortical thickening
High vertebrae

Age: 2 years Height: 77 cm (<<3° p)

- Weight: 8.150 Kg (<<3° p)
- HC: 50 cm (25°-50°p)

But no one has ever demonstrated digenic inheritance in 3M s.

First step in 2012: *CUL7* and *OBSL1* Sequencing 3M syndrome

SESSION 6 – EPONYMOUS SYNDROMES

16:30 FAMILIAL WHITE-SUTTON SYNDROME IN CHINESE

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White-Sutton syndrome is a rare neurodevelopmental disorder characterized by a wide spectrum of neurodevelopmental problems, hypotonia, seizures, refractive errors and strabismus, hearing loss, sleep disturbance, feeding and gastrointestinal problems. It is caused by pathogenic variant in POGZ gene. Here we have reported a familial case of White-Sutton syndrome in affected mother and affected son with novel variant heterozygous NM_015100.4(c.85_86del) in literature. Here summary the clinical features in the table as below.

	Mother	**Son**
Intellectual disability	+	+
Speech delay	-	+
Autism spectrum disorder	-	-
Hypotonia	-	+
Abnormal brain MRI	-	-
Microcephaly	+	+
Sensorineural hearing loss	-	-
Feeding problems	-	+
Obesity	+	-
Short stature	+	+
Intrauterine growth restriction	-	+
Brachydactyly	-	-
Broad thumb/hallux	-	-
Obstructive sleep apnoea	+	-
Strabismus	-	-
Hypermetropia	-	-
Myopia	-	-

16:40 BRYANT-LI-BHOJ NEURODEVELOPMENTAL SYNDROME 2, A CASE REPORT

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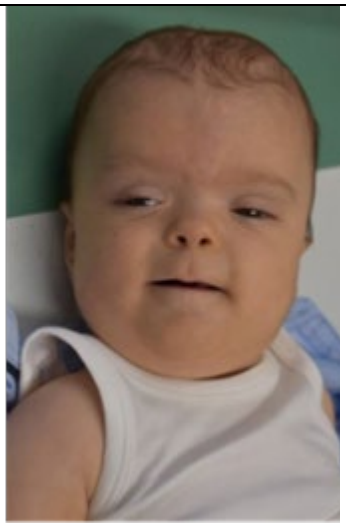
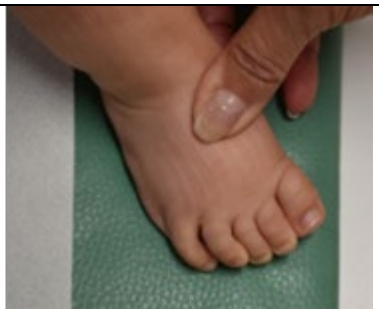
Somatic variants in Histone 3.3. (H3.3) are known promoters of oncogenesis. Germline pathogenic variants have been recently linked to a Bryant-Li-Bhoj neurodevelopmental syndrome 2, (MIM # 619721). Symptoms known to date include developmental delay, dysmorphic features with mostly minor congenital anomalies.
We present a 20-month-old proband, who was referred to us shortly after birth (born at 37+1 weeks of gestation), for IUGR, facial dysmorphism, hypoglycemia and necrotizing enterocolitis with bowel perforation.
Dysmorphic features at first evaluation were: hypertrichosis, dysplastic malrotated ears, very large anterior (4*4 cm) and posterior fontanelle, hypertelorism, broad thumbs, unilateral clubfoot, prominent processus xiphoideus.
Brain MRI revealed hypoplasia of the corpus callosum, enlarged subarachnoid space.
Family history is unremarkable, the parents of the proband are healthy as well as his 14-year-old sister.
We performed karyotype, aCGH and clinical exome analysis which were normal.
During the follow up the patient presented with delayed psychomotor development, bilateral sensorineural hearing loss, unilateral atrophy of the optic disc, strabismus, hypermetropy, plagiocephaly.
Brain MRI at the age of 10 months showed development of ventriculomegaly, the enlarged subarachnoid space and hypoplastic corpus callosum remained without change. No seizures to this day were observed.
We performed trio-Whole Exome Sequencing (WES) and found not yet described *de novo* likely pathogenic variant c.11C>T, p. (Thr4Ile) in *H3F3B.*
Our patient contributes another case to this relatively new *H3F3B* - related syndrome which has highly variable presentation thus further expanding the phenotype spectrum.


3 days


12 months



16:50 SULEIMAN-EL-HATTAB SYNDROME: IDENTIFICATION OF A NOVEL INTRAGENIC TASP1 DELETION AND CLINICAL PROFILING OF THE DISORDER

Davide Vecchio[1*], Marcello Niceta[2*], Marina Macchiaiolo[1], Cecilia Mancini[2], Luigi Chiriatti[2], Alessandro Bruselles[3], Maria Cristina Digilio[1], Andrea Bartuli[1], Marco Tartaglia[2]

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**equally contributed*

Suleiman-El-Hattab syndrome (SULEHS, OMIM #618950) is an ultra-rare autosomal recessive multisystemic developmental disorder characterized by early-onset hypotonia, feeding difficulties, global developmental delay, intellectual disability, and a general happy demeanor (1). While the condition shows microcephaly and a distinctive facial gestalt, additional variable features include brain, urogenital and cardiovascular malformations, axial and/or appendicular skeletal anomalies, and seizures (2,3). SULEHS is caused by biallelic loss-of-function variants of the *TASP1* gene, which encodes taspase-1, a threonine aspartase implicated in the activation of lysine methyltransferases, such as KMT2A and KMT2D, controlling histone methylation, chromatin remodeling and transcription (3). To date, a relatively small number of affected individuals have been reported (1-5), most of whom carrying intragenic deletions. Due to the rarity of the condition, the entire clinical profile of SULEHS is not fully characterized. Here, we describe a new patient with a novel homozygous intragenic 20.2kb deletion involving *TASP1* (chr20:13,433,274-13,453,514, GRCh38 assembly). The consanguineous healthy parents were proven to be carrier for the deletion (Fig. 1a). While the proband's features appeared to overlap with those that had previously been reported in SULEHS, we identified additional anomalies. These included (I) anatomic brain features (corpus callosum hypoplasia, cerebral convolutions' chaotic appearance, Rathke's cyst) (Fig. 1b), (II) skeletal defects (severe rotoscoliosis) (Fig. 1c), (III) enlargement of descending colon and sigma without transitional traits (Fig. 1d,e), and (IV) bladder duplication with extra Mullerian-type residues (Fig. 1f). The latter genitourinary and gastrointestinal features may belong the clinical complexity of SULEHS since they have sporadically been reported in other syndromes affecting the epigenetic machinery, such as Wiedemann–Steiner and Kabuki syndromes. Based on the relevant role of the protein in chromatin remodeling, validation of the disorder-specific DNA methylation signature is ongoing.

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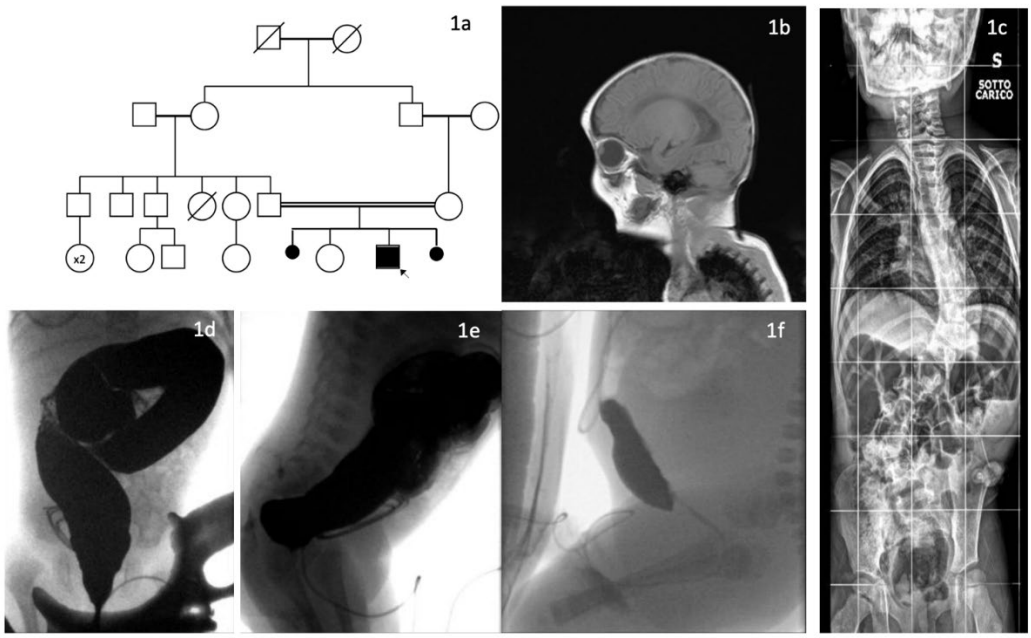

FIGURE 1: Our patient's family tree and major clinical features.

17:00 DE NOVO VARIANT IN SON GENE: CLINICAL EVALUATION AND GENOTYPE-PHENOTYPE OF ZHU-TOKITA-TAKENOUCHI-KIM SYNDROME.

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BACKGROUND. SON gene encodes a protein that plays an important role in cell cycle progression and is involved as a cofactor in the splicing process. Haploinsufficiency of this gene can lead to intron retention and omission of exons, which affects multiple genes, including several genes involved in development. Pathogenic variants in this gene are associated with Zhu-Tokita-Takenouchi-Kim syndrome (ZTTK) (OMIM #617140).

CASE PRESENTATION. We report the case of a 14 year old girl followed since infancy for pediatric neurometabolics and genetics due to : infantile hypotonia, develolpental delay , nistagmus and moderate intellectual disability .

She was born of non-consanguineous parents. No history of intellectual disability.
She was delivery at term weeks without complications.

Physical Examination: Weight: 38.5kg (-1.85 SD). Size: 156.5 cm (-0.89SD). Head: 54 cm (-0.96 SD).
Examination at 14y showed distinctive facial features with a prominent forehead, low-set ears, downslanting palpebral fissures, sparse eyebrows, , a flat nasal bridge, , a short nose, Her musculoskeletal features included long, slender extremities with joint laxity and arachnodactyly.Clinodactyly of 5th finger.

Investigations and Results: Neurometabolical studies were normal.

Electroencephalogram was normal. Brain MRI showed hypoplasia of the corpus callosum and small arachnoid cyst.

Chromosomal microarray: 11q25 deletion of 28.5 kb (VOUS)

Initially the first whole exome sequencing WES was normal.

After 5 years, Trio exome sequencing was done on the patient and both parents, and revealed de novo heterozygous frameshift variant in the SON gene OMIM (# 182465) which is classified as pathogenic variant according to ACMG recommendations. (NM_138927.4) c.5751_5754delAGTT, p.Val1918fs*87 .

The variant, detected in the patient's DNA, creates a premature translation stop signal in the SON gene and is expected to result in an absent or altered protein product.

This variant is not present in general population databases (gnomAD)

CONCLUSION: Pathogenic variants in this gene are associated with Zhu-Tokita-Takenouchi-Kim syndrome (ZTTK) (OMIM #617140) which was described in 2016 and whose clinical features mainly include developmental delay, brain malformations, facial dysmorphisms, ocular anomalies, urogenital malformations, and craniosynostosis

Here we emphasize the importance of imminent and repeated expanded genetic testing to ensure early diagnosis and triage for rare pediatric disorders. Because of regular updates in these panels, repeat genetic testing is worthwhile in children with undiagnosed. It has allowed us to provide appropriate management and genetic counseling to their families.

KEY WORDS: *SON*, intelectual disability, developmental delay, de novo variant.

17:10 PHENOTYPIC VARIABILITY IN WAARDENBURG SYNDROME TYPE I: A CASE REPORT OF A FAMILY WITH ATYPICAL PRESENTATION

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Waardenburg syndrome type I (WS1) is an autosomal dominant genetic disorder characterized by sensorineural hearing loss and pigmentary abnormalities of the iris, hair, and skin, often accompanied by dystopia canthorum. Here, we report the case of a proband and four other affected individuals spanning three generations within a family, all meeting clinical criteria for WS1. Clinical examination of the proband

revealed typical features including dystopia canthorum, sinophiris, and nasal abnormalities. Ophthalmological evaluation identified nasolacrimal duct obstruction, hypermetropia, anisometropia, and amblyopia. Genetic testing using the TruSightOne panel identified a heterozygous pathogenic variant, c.668G>A, in the PAX3 gene (NM_181458.4), confirming the molecular diagnosis of WS1. Interestingly, all five affected individuals lacked the typical sensorineural hearing loss phenotype, highlighting the phenotypic variability associated with this variant.

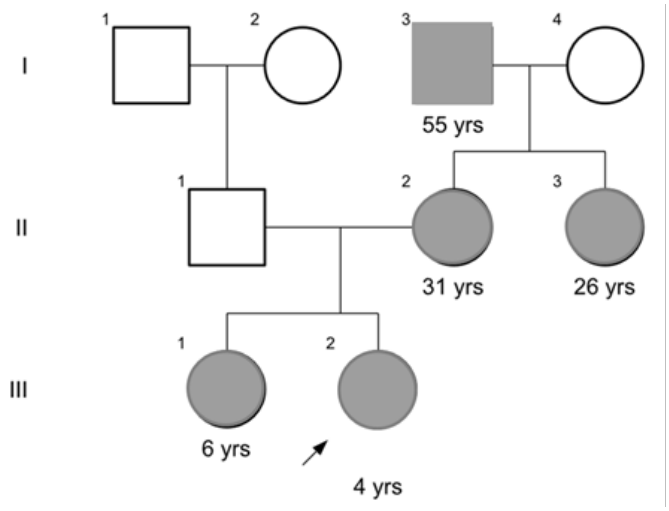

Figure 1. 3 generation pedigree

Figure 2. Proband with dystopia canthorum, with synophiris, wide nasal base, hypoplasia alae nasi

Table 1. Clinical criteria for Waardenburg syndrome and phenotype of 3 patients

The clinical diagnosis of Waardenburg Sdr. can be established based on [1]: **· 2 major criteria or** **· 1 major criterion and 2 minor criteria.**	**Patient III.2**	**Patient II.2**	**Patient I.3**
MAJOR CRITERIA			
· congenital sensorineural hearing loss	-	-	-

· hair hypopigmentation	-	-	-
· iris pigmentation anomalies: - complete iridian heterochromia - partial/segmental heterochromia - hypoplasia of the iris or bright blue eyes	-	-	-
· dystopia canthorum	+	+	+
· affected first degree relative	+	+	+
MINOR CRITERIA			
· skin hypopigmentation	-	-	-
· synofris	+	+	+
· the root of the nose is wide, the columella is low	+	+	+
· hypoplasia alae nasi	+	+	+
· premature graying (<30 years)	-	+	+

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17:20 COHEN SYNDROME, A NOVEL VARIANT IN TWO SIBLINGS WITH A HETEROGENEOUS PHENOTYPE

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Introduction*:* Cohen syndrome is an autosomal recessive inherited disorder, characterized by global developmental delay, progressive microcephaly, hypotonia and feeding problems. As the disease progresses, obesity, retinochoroidal dystrophy and myopia may occur.

Cases*:* We report two siblings from consanguineous parents of Afghan descent.

The index patient, a boy born at term with a normal birth weight, was referred for genetic counseling of failure to thrive and a global developmental delay (age 2.5 years). He had a slightly delayed motor development (walking 1,5-2 years), near absent speech, and a short stature (although within target height range).

Measurements: Height -3 SD, weight for height -2.4 SD and Head circumference -2 SD (Dutch reference values).

Facial features: Long face with epicanthal folds, full eyebrows. There was a short philtrum and a small mouth with widely spaced teeth.

Laboratory tests revealed a neutropenia, but there were no recurring or severe infections. Ophthalmological evaluation: hypermetropia and astigmatism, normal retinae.

Currently (age 4 years), his developmental delay is more prominent with poor cognitive abilities. Although there is no progressive microcephaly (-1,8 SD).

His younger brother was seen at our department at the age of 10 months. He was born term with a normal birth weight, and a head circumference at birth of -0.5 SD. His development was normal.

Measurements: Height -2.6 SD, weight for height -1 SD and Head circumference -3.1 SD.

Facial features: Round face with epicanthal folds, full arched eyebrows and folded helices of the ears. There was a small mouth, similar to his older brother, retrognathia and microcephaly. There was a mild neutropenia without recurring or severe infections and ophthalmological evaluation was normal.

Currently at the age of 14 months, his neurodevelopment seems near normal. With respect to the progressive microcephaly, brain imaging is pending.

Genetic testing: Whole exome sequencing revealed a homozygous, biallelic, variant in the *VPS13B* gene c.11973_11976dupAACA, p.(Tyr3993Asnfs*7). Moosa et al. reported two siblings with a homozygous truncating variant in the same exon, and with a phenotype concurrent with Cohen syndrome.[1] Subsequently, the variant identified in our patients was graded as a class 4 likely pathogenic variant.

Conclusion: We identified a novel variant in the *VPS13B* gene, causing Cohen syndrome. Our patients illustrate a heterogeneous phenotype within a family with a striking difference in the progression of microcephaly. With the young age, the evolution of weight, development and retinae is yet unclear.

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17:30 COFFIN-SIRIS SYNDROME: CLINICAL DESCRIPTION OF TWO COLOMBIAN CASES

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Coffin-Siris syndrome (CSS) is a rare genetic disorder characterized by developmental delays, intellectual disability, distinctive facial features, and abnormalities of the fingers and toes. There are fewer than 500 reported cases with molecular confirmation worldwide; therefore, due to the scarcity of cases, the exact prevalence and incidence are unknown, with a global prevalence estimated at <1/1000000. Additionally, in Colombia, only a few reported cases, and the exact prevalence and incidence are not well-established.

We present two Colombian male patients attending medical genetic consultation in Bogotá-Colombia with a diagnosis of Coffin-Siris syndrome with pathogenic variants in the SOX11 and SMARCA4 genes by exomic sequencing technique.

SOX11 acts as a transcription factor that regulates the expression of other genes during development. Pathogenic variants in SOX11 are believed to alter gene expression regulation during embryogenesis, leading to the symptoms observed in CSS. On the other hand, the SMARCA4 gene encodes a subunit of the SWI/SNF protein family, which are chromatin remodeling complexes. At the molecular level, mutations in SMARCA4 can affect the ability of the SWI/SNF complex to remodel chromatin, resulting in changes in gene expression during development and contributing to CSS symptoms.

The following two cases show the wide variability in the phenotypic spectrum of presentation of Coffin-Siris syndrome, at one extreme we have a patient with a pathogenic variant in SMARC4 with a marked cognitive deficit and a notorious facial dimorphism, while at the other extreme we see a patient with an attenuated phenotype with tall stature and hypogonadism with borderline intelligence, which shows a possible genotype-phenotype correlation.

In summary, Coffin-Siris syndrome is caused by mutations in genes involved in chromatin remodeling and requires multidisciplinary care to manage its various manifestations.

Syndromes like CSS highlight the importance of gene function and their special role during embryological development, providing insight into pathophysiology.

Friday 20th of September

SESSION 7 – SYNDROME DELINEATION

09:00 UNRAVELING AN ULTRA RARE OBESITY SYNDROME: NTRK2 MUTATIONS IN TWO BRAZILIAN PATIENTS WITH MACROSOMIA, OBESITY, MACROCEPHALY AND OCULAR ABNORMALITIES (MOMO) SYNDROME

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Background: MOMO syndrome is an extremely rare genetic disorder. The name is an acronym of the four primary aspects of the disorder: macrosomia, obesity, macrocephaly and ocular abnormalities (OMIM 157980). First described in two unrelated patients in 1993 by Moretti-Ferreira et al., it was suggested to be due to an autosomal dominant mutation. MOMO syndrome is considered to be a multisystemic genetic disease, and overall is associated with obesity.

Material and Methods: Retrospective cohort study of 80 Brazilian patients with syndromic obesity referred to a national centers for rare diseases in Brazil. All patients underwent genetic tests with a customized Next Generation Sequencing (NGS) panel in combination with biochemical testing (organic acids and amino acids chromatography, acylcarnitine profile, 3OMD dosage, prolactin, blood lactate, CK, homocysteine, among others) in a 2 year period. As inclusion criteria, patients should have intellectual disability/developmental delay, hyperphagia, normal genetic testing for Prader-Willi syndrome and obesity onset in the first two years of life.

Results: Overall, pathogenic and possibly pathogenic variants were detected in 43/80 patients (57%). Among them, we found two cases harboring possibly pathogenic variants in the NTRK2 gene. Both patients fulfilled criteria not only for syndromic obesity , but in particular for MOMO syndrome, showing neurological features already reported in this condition, including autism spectrum disorder.

Discussion: Moretti-Ferreira et al. [1993] described two unrelated Brazilian patients of both sexes with a combination of macrosomia, macrocephaly, obesity, ocular abnormalities (retinal coloboma and nystagmus), downward slant of the palpebral fissures, intellectual disability (ID), and delayed bone maturation. Thereafter the new syndrome called MOMO was categorized as an overgrowth syndrome [Cohen, 2002]. However, a third patient published in 2000 had short stature and overgrowth was discussed as non-mandatory for the diagnosis. It remains unclear if overgrowth is a mandatory finding as ocular abnormalities can also be very comprehensive and most patients reported so far do not show coloboma, although strabismus and nystagmus are usually frequent. Our patients showed the core features of the disease confirming also an autosomal pattern of inheritance.

Conclusions: Developmental and epileptic encephalopathy and Obesity, hyperphagia, and developmental delay (OBHD) are two conditions previously linked to NTRK2 gene mutations. OBHD is a rare neurodevelopmental genetic disorder with only 5 patients published so far and it is characterized by obesity and a generalized developmental delay especially cognitive and verbal. Macrosomy and macrocephaly was not reported in such patients, however some ocular features were described in a subset of patients. Our findings suggest that MOMO and OBHD can be allelic disorders and patients with a former diagnosis of MOMO syndrome should be screened for NTRK2 mutations.

09:15 POU3F2 GENE VARIANT IN A MELANESIAN BOY WITH INTELLECTUAL DEFICIENCY AND HYPERPHAGIC OBESITY

Didier LACOMBE[1], Isabelle Missotte[2], Mélanie Fourgeaud[1], Ria Schoenauer[3], Vincent Michaud[1], Jan Halbritter[3].

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[3] Charite University Hospital Berlin, Berlin, Germany.

Monogenic obesities are commonly associated with central nervous dysregulation of food intake and satiety. It is often supported by neurodevelopmental delay (NDD) and autism-spectrum disorder. *POU3F2* gene, encoding a neural transcription factor, has been suggested to be driver of obesity and NDD in individuals with the chromosome 6q16.1 deletion syndrome. An international collaboration identified 10 *POU3F2* variants associated with this phenotype (Schoenauer et al., Am J Hum Genet 2023, 110(6):998-1007).

We report a male case (G.N.) from New Caledonia Island. The patient present a Prader-Willi-like phenotype including intellectual disability (ID), autism, and severe hyperphagic obesity (BMI > 35 kg/m²). G.N. is the first child of non-consanguineous parents. Family history is not informative. He had an healthy younger brother. Pregancy and delivery were normal. Hypotonia and developmental delay were noticed in the first year of life. The child walked alone at age 19 months. A severe speech retardation was present at age 5 years. Physical examination showed strabismus and minor facial features including round face and large ears. At age 13 years, height was 165 cm, weight was 96.3 kg (BMI = 35.37 kg/m²), and OFC was 57.5 cm (+ 2.5 SD). He was hyperphagic and showed a mil ID.

Physical examinations (brain MRI, abdomino-renal and cardiac ultrasound examinations) and genetic analysis (blood chromosome analysis, array-CGH, fragile X and Prader-Willi specific testing) were normal. Exome sequencing noticed a *de novo POU3F2* gene variant (c.1064G>T ; p.(Arg355Leu)), affecting one of the two DNA-binding-POU-domain. Insuline and leptine serum dosages showed elevated values.

POU3F2 encodes a transcription factor which regulates a large number of target genes including genes involved in monogenic obesity (*LEPR*, *MC4R*, *PCSK1*, *BBS7*). POU3F2 trancriptional factor activity is supposed to interact within the central nervous system, regulating eating behavioral process.

09:25 NATURAL HISTORY OF ADULTS WITH KBG SYNDROME: A PHYSICIAN-REPORTED EXPERIENCE

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Purpose: KBG syndrome (KBGS) is a rare neurodevelopmental syndrome caused by haploinsufficiency of *ANKRD11*. The childhood phenotype is extensively reported but limited for adults. Thus, we aimed to delineate the clinical features of KBGS.

Methods: We collected physician-reported data of adults with molecularly confirmed KBGS through an international collaboration. Moreover, we undertook a systematic literature review to determine the scope of previously reported data.

Results: The international collaboration identified 36 adults from 31 unrelated families with KBGS. Symptopms included mild/borderline intellectual disability (n=22); gross and/or fine motor difficulties (n=15); psychiatric and behavioral comorbidities including aggression, anxiety, reduced attention span, and autistic features (n=26); nonverbal (n=3), seizures with various seizure types and treatment responses (n=10); ophthalmological comorbidities (n=20). Cognitive regression during adulthood was reported once. Infrequent features included dilatation of the ascending aorta (n=2) and autoimmune conditions (n=4). Education, work, and residence varied and the diversity of professional and personal roles highlighted the range of abilities seen. The literature review identified 154 adults reported across the literature, and we have summarized the features across both datasets.

Conclusion: Our study sheds light on the long-term neurodevelopmental outcomes, seizures, behavioral and psychiatric features, and education, work, and living arrangements for adults with KBGS.

09:40 GENETIC AND CLINICAL CHARACTERIZATION OF KBG SYNDROME: A CASE REPORT

09:50 DESCRIPTION OF A FRENCH COHORT OF MALE FORMS OF BPAN (X-LINKED NBIA) AND REVIEW OF THE LITERATURE

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Beta-propeller protein-associated neurodegeneration (BPAN) is an ultra-rare form of neurodegeneration with brain iron accumulation (NBIA). This X-linked dominant disorder results from pathogenic variants in WDR45, encoding for the WD45 repeat domain or WIPI4, involved in cellular autophagy. BPAN is primarily described in females with a few reported male cases to date. Pathogenic variants in WDR45 in male patients typically occur de novo or from germinal mutations inherited from an unaffected mother. Less commonly, cases of postzygotic somatic mosaicism have been reported but remain poorly understood. Disease manifestations tend to be more severe in males. The progression is generally biphasic: developmental in

childhood marked by developmental delay and motor disorder followed by progressive worsening with dystonia and parkinsonism in adolescence/adulthood. Epilepsy is common, and susceptibility-weighted imaging (SWI MRI) may inconsistently reveal iron deposition in the basal ganglia.

In collaboration with neurogenetic reference centers in France, we have established a multicentric retrospective cohort of 7 finely phenotyped male BPAN cases. For these, we have collected electro-clinical data, brain imaging (MRI), and genetic data. We have particularly focused on the electro-clinical phenotype and the repercussions of the second phase on the patient's autonomy and family environment.

Here we present our findings from this unique cohort of male forms of BPAN in France.

10:05 DMRT1 MISSENSE VARIANT CAUSING FAMILIAL 46,XY GONADAL DYSGENESIS

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We present two sisters with 46,XY gonadal dysgenesis. The proband presented aged 16 years to the General Practitioner with poor breast development. Menses hadn't yet commenced. Biochemical investigation were consistent with gonadal failure (LH 19.7iU/L(<13.1), FSH 82.6iU/L (0.3-7.7), estradiol <37pmol/L(<936), testosterone 0.9nmol/L ().4-1.7), AMH <0.07pmol/L). and subsequent Karyotype revealed 46,XY. MRI pelvis revealed a rudimentary uterus, no ovarian tissue was identifiable.

The family history revealed 3 sisters, an older sister had a normal puberty and regular menstrual cycle. Two younger sisters; aged 13 & 14 years, had not yet developed menses and neither had breast development.

Trio exome revealed a missense variant c.315C>G; p.CYs105Trp in the proband in DMRT1 described as a variant of unknown significance.

Karyotype analysis was performed on the two younger sisters. The 14 year old was shown to have 46,XY karyotype, high LH and FSH with undetectable oestradiol and small gonads on pelvic ultrasound and, the familial DMRT1 variant is currently being analysed. The younger 13 year old sister has a 46,XX karyotype but her pelvic ultrasound showed her uterus and ovaries were present and LH/FSH & oestradiol were normal.

The mother was found to be mosaic (52%) for the variant.

DMRT1 is a male-specific transcriptional regulator and is a key factor in sex determination and differentiation. Its association with 46,XY gonadal dysgenesis was first noted in patients with deletions of chromosome 9p24.3. The gene is sex specific. So far, very few variants have been reported and the phenotype ranges from phenotypic males with infertility through to phenotypic females with XY gonadal dysgenesis. Murphy *et al*. reported the first point mutation of *DMRT1* in a 46,XY complete gonadal dysgenesis patient, and showed the heterozygous mutant affects DNA binding affinity and results in a severe phenotype. This heterozygous variant was transmitted from the unaffected mother. As DMRT1 is only expressed in male-specific gonads, it is possible that the variants in DMRT1 do not affect ovarian development, thus female carriers do not have a phenotype.

Management will require removal of gonads in both sisters as there is a small malignant transformation risk.

10:15 COMPREHENSIVE DESCRIPTION OF A NEONATE WITH MIDLINE ANOMALIES AND SITUS INVERSUS

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We describe the clinical presentation, radiological findings, and genetic investigations of a neonate exhibiting multiple congenital anomalies, primarily affecting midline structures and associated with cardiovascular and abdominal abnormalities. Clinical examination and radiological assessment revealed a non-separation of the incisors, stenosis of the piriform apertures, and a bilateral severe hypoplasia of olfactory bulbs. He also presented with the absence of the left carotid canal with severe hypoplasia of the left internal carotid artery, a compensatory circulation through the anterior communicating artery supplying the middle cerebral artery. The echocardiogram reveals a high ventricular septal defect with a septo-aortic offset, associated with an ostium secundum atrial septal defect. Additionally, the patient presented with abdominal situs inversus without malposition of the mesenteric vessels. Prenatal aCGH was unremarkable and postnatal genetic testing included a trio genome sequencing. We will present herein the clinical and radiological description and discuss the pathophysiological hypotheses for this patient with a polymalformative syndrome.

Keywords: Midline anomalies, partial incisor non-separation, carotid canal agenesis, olfactory bulb hypoplasia, ventricular septal defect, situs inversus

SESSION 8 – SYNDROME DELINEATION

11:45 SKELETAL DYSPLASIA WITH AMELOGENESIS IMPERFECTA IN TWO SIBLINGS HARBORING BIALLELIC PATHOGENIC MISSENSE VARIANT IN SLC10A7 GENE

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Homozygous or compound heterozygous mutations in the Solute Carrier Family 10 (Sodium/Bile Acid Cotransporter Family), Member 7 (*SLC10A7*, MIM#611459) gene cause Short Stature, Amelogenesis Imperfecta, and Skeletal Dysplasia with Scoliosis (SSASKS, MIM#618363). According to Nosology and Classification of Genetic Disorders of the Skeleton 2023 revision, it is grouped under “Group 5-Dysplasias with multiple joint dislocations". To our knowledge, 9 individuals with pathogenic biallelic variants in *SLC10A7* gene have been reported so far. Affected individuals display dysmorphic features, such as dental abnormalities, severe pre- and postnatal disproportionate short stature, multiple dislocations with monkey

wrench appearance of the proximal femora, shortened long bones with metaphyseal widening, and advanced carpal and tarsal bone age. Herein, we describe two siblings with disproportionate short stature and amelogenesis imperfecta due to a pathogenic biallelic missense variant in *SLC10A7* gene. The first case was a 4-year and 9-month-old boy who referred to our department for short stature, kyphoscoliosis, joint laxity, and distinctive facial findings. The patient was the third live-born child of first cousin parents following a 36th gestational week pregnancy with a birth weight of 2,600 gr (-0,23 SDS). Birth length and occipitofrontal circumference (OFC) were not noted. At the 20th gestational week, prenatal ultrasonography revealed shortening of the long bones and macrocephaly. The patient had respiratory distress requiring neonatal intensive care unit support. He was discharged without respiratory assistance on the postnatal 15th day. Before admission to our center, he had been evaluated for growth retardation and characteristic facial features. Karyotype analysis was consistent with 46, XY, and FGFR3 sequence analysis was normal. Physical examination at his admission revealed a body length of 81 cm (−6.32 SDS), weight of 10.2 kg (-5.09 SDS), and OFC of 40 cm (-3.03 SDS). He had a round flat face, a high forehead with prominent metopic suture, epicanthus on the left eye, bilateral proptosis, a short nose, a long philtrum with a thin upper lip, microstomia, and retromicrognathia. A short neck, a single palmar crease on the left hand, joint laxity without dislocations, and kyphoscoliosis were also noted. In addition, hypo-mineralized amelogenesis imperfecta and bilateral fundus atrophy were detected on eye and dental examination. Abdomen ultrasound was normal yet echocardiography showed tricuspid insufficiency. Plain radiograms revealed shortened long bones with metaphyseal widening, genu valgus, advanced carpal ossification, and thoracolumbar levoscoliosis. Epiphyseal anomalies were not observed. The iliac bones were broad and round and the acetabula were shallow as well. The Denver Developmental Screening Test II (DDSTII) was compatible with retardation except for the language. His sibling,19 years old, underwent several operations for kyphoscoliosis, had similar facial gestalt and radiological findings. Based on these a clinical diagnosis of SSASKS was made on clinical and radiological grounds. Next-generation sequence analysis identified a *SLC10A7* pathogenic biallelic variant (NM_032128.4): c.221T>C, p.Leu74Pro) in exon 3. This change was previously reported in the Turkish population. Notably, dental abnormalities have not been described so far for this dysplasia group; hence, amelogenesis imperfecta can be suggested as a new clinical feature indicative of *SLC10A7* mutations. We believe that as more patients are reported in the literature, the phenotypic features of the disease and the genotype-phenotype correlation can be more accurately defined.

Figure Legends

Fig.1 AP spine radiograph reveals thoracolumbar levoscoliosis, rounded iliac wings with flattened acetabular roofs.

Fig. 2 PA chest radiograph shows bilateral shortened humerus with widened distal metaphysis and mild diaphyseal irregularity.

Fig. 3 Lateral skull radiograph showing flattened face with mild retromicrognathia.

Fig. 4 Bilateral femur radiographs of the present case (a) and a healthy boy at the same age. Please note that widened metaphyses were more prominent in the present case than in the control.

Fig. 5 Hand radiograph of the present case (a) and healthy control (b) at the age of 4-year and 9-month-old. Advanced bone age was a striking feature compared to the healthy control.

Fig. 1

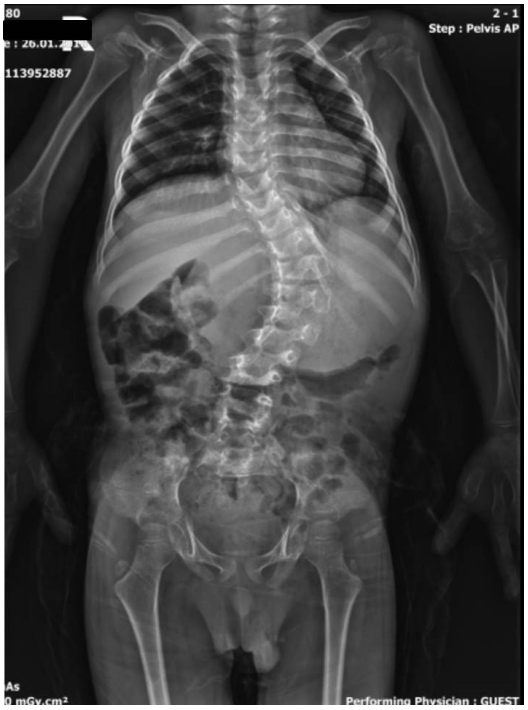


Fig. 2

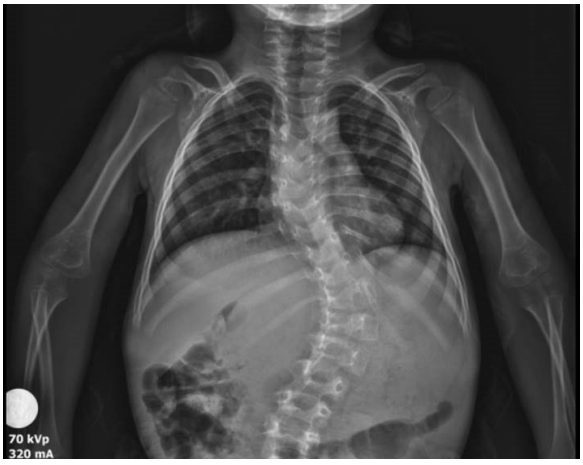


Fig. 3

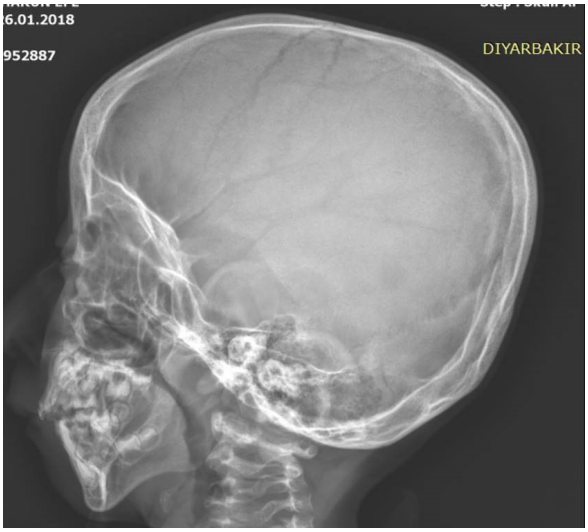


Fig. 4

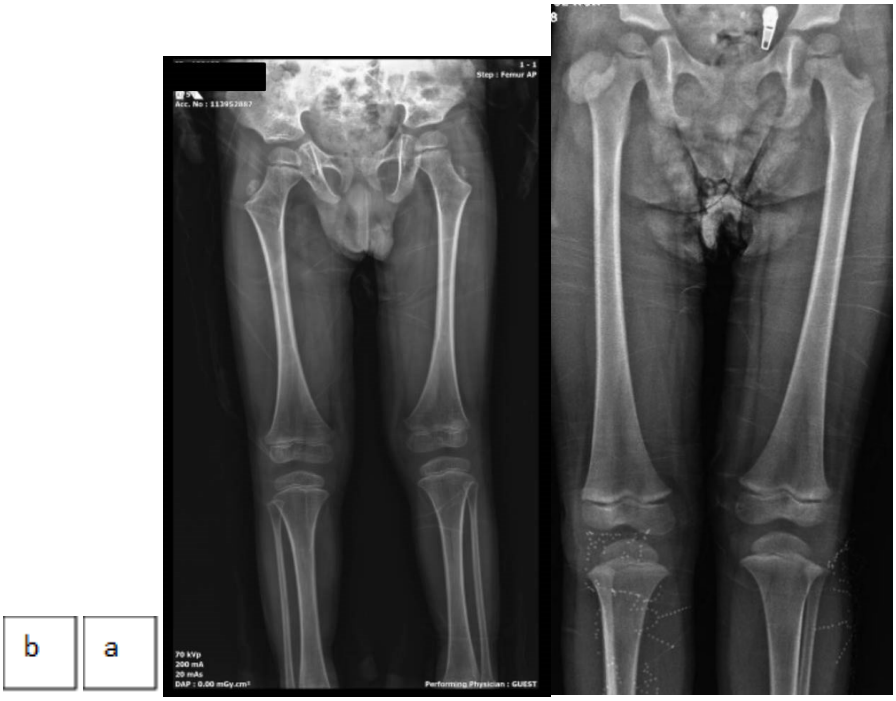
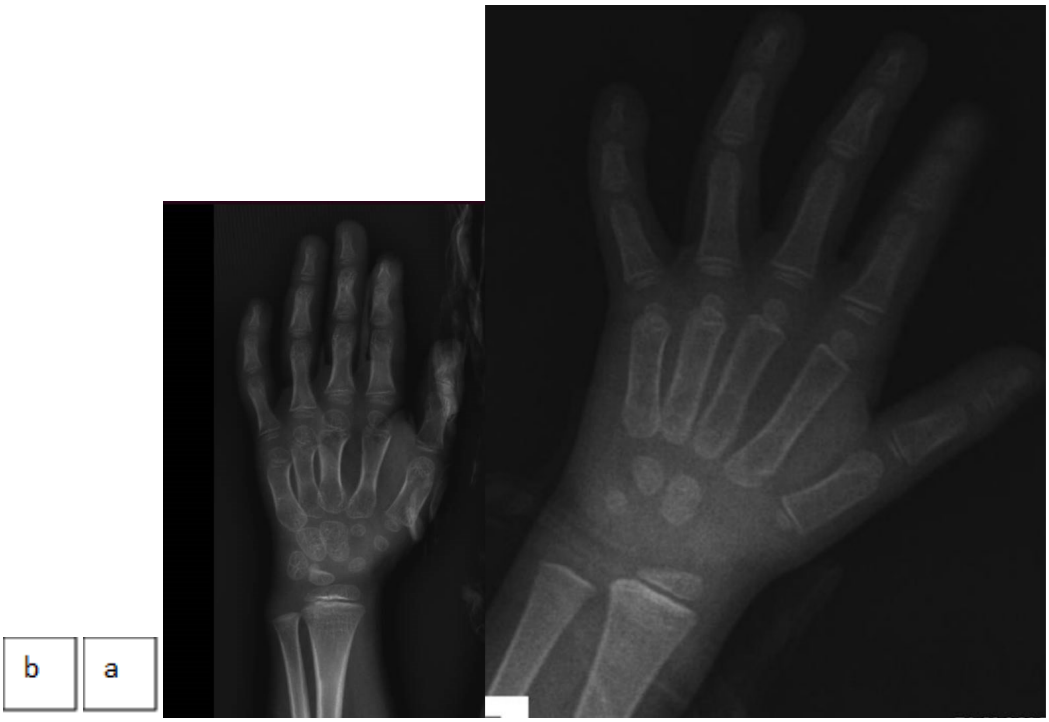


Fig. 5



11:55 A NOVEL HETROZYGOUS DNM1L VARIANT ASSOCIATED WITH LETHAL ENCEPHALOPATHY

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Background: Epilepsy-associated neurodevelopmental disorders include several mitochondrial diseases (MDs). In MDs, any seizure type can occur, the most common being myoclonus, focal motor seizures with secondary generalization and generalized tonic-clonic seizures, whereas the rarest are classical absences.

Clinical history. Twelve years after her death, a baby girl received her genetic diagnosis, when the father asked his reproductive risk. The patient was referred to us at 16 months of age for psychomotor delay, congenital microcephaly and fine tremors in the limbs. At that time brain MRI and EEG recordings were unremarkable, whereas lactic acid values were elevated in blood and liquor.

At 26 months she developed drug-refractory myoclonic epilepsy evolving in status epilepticus. The patient came tetraparetic and suffered of episodes of blood oxygen desaturation; nasogastric tube was applied for feeding as well as CPAP to prevent sleep apnea. Brain MRI showed a rapidly evolving cortico-subcortical atrophy. Ultrasound of the heart and abdomen were normal.

She died at the age of 36 months. Post-mortem autopsy revealed hypertrophic cardiomyopathy, spongiosis, gliosis, areas of neuronal loss and necrosis.

The proband was wild-type for *POLG* variants and molecular karyotype. Muscle histology and activity of the muscle mitochondrial respiratory chain were normal.

Results: Trio-WES analysis on DNA extracted from the patient's muscle biopsy and DNA extracted from both parents' blood allowed us to identify in the proband a *de novo* heterozygous *DNM1L* variant (NM_001278464.1):c.1240G>A, p.(Gly414Ser).

Discussion: Pathogenic variants in *DNM1L* cause **'**Encephalopathy, lethal, due to defective mitochondrial peroxisomal fission 1' (OMIM # 614388). *DNM1L*-related mitochondrial diseases had been rarely reported to cause a severe neurological phenotype, including epilepsy (59.4%), psychomotor retardation, limb paralysis, dystonia, ataxia, nystagmus, optic atrophy, dysarthria, microcephaly, pain insensitivity, and sensory and motor axonal neuropathy. The median age of onset was 6 months (from birth to 9 years).

We identified a novel *DNML1* variant classified as likely pathogenetic according to ACMG criteria. The *DNM1L*(NM_001278464.1):c.1240G>A, p.(Gly414Ser) is located in the middle domain of DRP1. Albeit rare, patients who have mutations in this domain exhibit epilepsy more frequently than those carrying mutations elsewhere. *DNML1* is a major component of the mitochondrial fission system. Elongated, spaghetti-like organelles are typically present in *DNM1L* mutations; morphological examination of the shape and structure of mitochondria are underway in the present case. NGS sequencing for molecular diagnosis can reveal the presence of *de novo*, lethal encephalopathies, also in deceased patients. *DNML1 de novo* mutations must be considered as candidates in severe myoclonic epilepsy associated with acquired brain atrophy as well as in children exhibiting early psychomotor retardation with microcephaly

12:05 A RAPRESENTATIVE CASE OF PHENOCOPY OF WILLIAMS SYNDROME DUE TO PATHOGENIC TBR1 VARIANTS AND LITERATURE REVIEW

Federica Anna Pirro[1], Irene Bottillo[1], Luigi Laino[1], Niccolò Di Giosaffatte[1], Barbara Grammatico[1], Paola Grammatico[1] and Francesca Clementina Radio[1]

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Williams syndrome (WS) is a rare genetic disorder characterized by neurodevelopmental delay (NDD)/intellectual disability (ID), typical behavioural profile, growth delay, cardiovascular disease, connective tissue abnormalities, and distinctive facies.
The condition is usually due to a heterozygous 1.5- to 1.8-Mb deletion of the critical chromosomal region 7q11.23. Nevertheless, a subset of individuals reaching the WS diagnostic criteria remains undiagnosed. Several genes are currently under evaluation as causative of WS-like phenotypes.
We describe a 5-year-old female affected by NDD/ID with typical behavioural anomalies (e.g. hypersocial behaviour, hyperacusis) and distinctive dysmorphic features (i.e., broad forehead, bitemporal narrowing, epicanthal fold, periorbital fullness, stellate iris pattern, short nose, broad nasal tip, malar flattering, full cheeks, long philtrum, thick vermilion of the upper and lower lips and wide mouth). No major malformation was noted. WS was clinically suspected without chromosomal microarray (CMA) confirmation. Whole exome sequencing revealed a likely pathogenic variant affecting the TBR1 gene, known to cause a spectrum of neurodevelopmental disorders with behavioural abnormalities collectively termed IDDAS. To date, no recognizable craniofacial profile had been reported for IDDAS.
Based on systematic review of 25 affected individuals and iconographic data of 12 patients, a recurrent and recognizable craniofacial appearance associated with IDDAS, very similar to WS, was identified. This includes features such as a broad forehead (11/13), bitemporal narrowing (7/13), strabismus (8/13), epicanthal folds (7/13), short nose (6/13), broad nasal tip (9/13), malar flattening (7/13), full cheeks (9/13), long philtrum (10/13), wide mouth (6/13), and large ear lobes (7/13). Along with the physical characteristics, it has been noted that the behavioral characteristics also appear to be comparable with WS, at also in both conditions there is an involvement of the connective tissue and/joint hypermobility. On the other hand, no major malformations nor cardiovascular disease have been reported in IDDAS to date.
These findings suggest the existence of a phenocopy of Williams syndrome, referred to as IDDAS, which may be considered as a potential differential diagnosis for CMA negative WS. The study aims to gather additional cases to further characterize IDDAS and, eventually, establish clinically relevant genotype-phenotype correlations.

12:15 OCULO-FACIO-CARDIO-DENTAL SYNDROME: A NOVEL VARIANT AND AN EXPANSION OF THE PHENOTYPE

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Background: Oculo-facio-cardio-dental syndrome (MIM #300166) is an X-linked syndrome caused by pathogenic heterozygous variants in the *BCOR*-gene at chromosome Xp11.4 (Ng et al 2004). BCOR is a part of the control of geneexpression in multiple tissues and is widely expressed with spatial and temporal differentiation during embryogenesis (Huynh et al 2000, Wamstad et al 2007).

Clinical features of the syndrome is congenital cataract, microphthalmia, distinctive facial features as a long narrow face, broad or septate nasal cartilage, congenital heart defects and dental abnormalities (Ragge et al. 2019)

Case: We present a 25-year old Caucasian female with a novel BCOR variant and both classical features of OFCD and previously less or undescribed phenotypic features, possibly linked to the syndrome.

The patient is born with bilateral congenital cataract, nanophthalmia and blindness of the left eye and she developed glaucoma in the early youth. She had hyperdontia of the incisives, persistent primary dentition and repeating odonatological procedures including removal of primary teeth and rearrangement of permanent dentition.

Her facial features includes a long, narrow face, pear shaped nose with low hanging columella and a broad nasal tip cartilage. As a child, she had cup-shaped, protruding, low set ears and she had aures alatae surgery. She has a congenital palate-pharyngeal insufficiency and a bifid but not septate uvula. She has syndactyly of 2^{nd} and 3^{rd} toe on the left side and an atrial septal defect.

An exome based eye malformation panel showed heterozygosity for a novel BCOR c.2048del p.Pro683Glnfs*32, a likely pathogenic variant (C4). The variant is presumed to cause a frame shift leading to a premature stop codon. The variant has not been reported earlier for patients with microphthalmia, cataract or in healthy controls (gnomAD v2.1.1)

She has had a congenital neck mass in the midline of the neck. It was surgically removed and the histopathological type was a thyroglossal duct cyst. Due to symptoms of polycystic ovaries, she got a transvaginal ultrasound showing bicorn uterus, which was confirmed on an MRI when she was 24 years old.

Conclusion: We present a novel pathogenic BCOR variant in a female with the classical phenotype, and further a thyroglossal duct cyst and a bicorn uterus. Thyroglossal duct cysts is previously described in one patient with OFCD. Bicorn uterus is previously undescribed but taking BCOR's role in embryogenesis in consideration, it could be a part of her OFCD syndrome.

12:25 ATTENUATED FORM OF NIJMEGEN BREAKAGE SYNDROME: CASE REPORT

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Nijmegen Breakage Syndrome (NBS, MIM #251260) is a rare DNA repair disorder characterized by microcephaly, growth retardation, dysmorphic features, immunodeficiency, and predisposition to cancer. NBS results from biallelic pathogenic variants, predominantly truncating, in the *NBN* gene, which plays a role in the homologous recombination pathway. Impaired DNA repair mechanisms typically present with malignancies at an early age. The prognosis of NBS is generally poor due to early onset malignancies, unfavorable responses to treatment, and a high incidence of treatment-related secondary hematological malignancies. Although NBS is known as a life-limiting disorder due to its poor prognosis, some individuals with atypical presentations have been documented.

We report a case of a 69-year-old male diagnosed with prostate cancer six years ago, who was referred to our outpatient clinic to investigate a possible genetic etiology of familial cancer predisposition.

He was the fourth live-born child of first-cousin parents. His mother was diagnosed with colorectal cancer at age 60. Three of his sisters were diagnosed with malignancies; one with lymphoma at age 50, and the others with thyroid cancer at ages 35 and 55. His father's and three children's medical histories were uneventful. Besides oncological issues, he had severe pneumonia around the age of seven and frequent coughs and sinusitis throughout his adult life. He had never been diagnosed with any other hematological, immunological, or oncological issues. His intellectual capabilities were normal, and he was retired from civil service. During the physical examination, his anthropometric measurement were within normal ranges. Additional observations included facial rash, freckling, and irregular hyperpigmented macules. His basic biochemistry and full blood counts were within normal ranges.The next-generation sequencing panel test (Hereditary Cancer Solution v2.0, SOPHiA, Switzerland) identified the c.1894C>T p.(Arg632*) pathogenic variant in the *NBN* gene (NM_001024682.2) in the homozygous state. Chromosomal analysis was normal.

Although the patient was not diagnosed with a malignancy at an early age and his head circumference was within the normal range, the history of malignancies in his family, along with his skin lesions and mild immunodeficiency, are consistent with NBS. Only three mild cases of NBS have been reported in the literature to date. Based on our knowledge, our patient is the oldest documented individual with NBS. This case is distinct in his fertility, chromosomal analysis, and skin lesions. Several mechanisms could explain this mild clinical presentation, including the location of the variant in the gene and its effect on protein function. Our case might represent an attenuated form of NBS. This report aims to broaden our understanding of this rare phenotype and the clinical spectrum of the syndrome.

12:35 A SEVERE CASE OF HYPERPHOSPHATASIA WITH MENTAL RETARDATION SYNDROME AND MYELODYSPLASTIC SYNDROME

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Hyperphosphatasia with mental retardation syndrome-1 (HPMRS1, OMIM # 239300) is caused by biallelic variants in *PIGV*, a gene involved in the glycosylphosphatidylinositol (GPI) biosynthesis. The rare syndromic disorder is characterized by impaired intellectual development, seizures, and muscular hypotonia. Other features include hyperphosphatasia, variable degrees of brachytelephalangy, and facial dysmorphism.

Pediatric myelodysplastic syndromes (MDSs) are a heterogeneous group of clonal disorders accounting for less than 5% of childhood hematologic malignancies and often occur in the context of inherited bone marrow failure syndromes. Germline mutations predisposing individuals to develop MDS or acute myeloid leukemia have recently been identified, such as those caused by variants in *GATA2*, *ETV6*, *SRP72*, and *SAMD9/SAMD9-L.*

Here, we report a 15 years old clinically severely affected boy, presenting with dysmorphic facial features typical for HPMRS1, including cleft palate, short philtrum, downturned corners of the mouth, hypertelorism, upslanting, long palpebral fissures, and arched eyebrows. He also had severe psychomotor retardation with

hypotonia, hydrocephalus, macrocephaly, hearing impairment, renal malformations and Hirschsprung's disease.

GestaltMatcher suggested HPMRS1 and whole genome sequencing revealed the pathogenic variants NM_017837.4: c.439C>T p.(Gln147*) and c.1022C>A p.(Ala341Glu) in *PIGV.* These variants are known to underpin a severe HPMRS1 phenotype.

Notably, the patient developed thrombocytopenia and his bone marrow showed changes interpreted by the national reference pathologist as MDS of the refractory cytopenia of childhood (RCC) type, the most frequent pediatric MDS variant.

Despite excluding paroxysmal nocturnal hemoglobinuria (PNH) via repeated flow cytometric analysis, the co-occurrence of MDS and GPI anchor deficiency may hint at a potential interplay in disease progression. Yet, the genesis of MDS remains elusive, with plausible ties to the severe *PIGV* variants warranting further exploration.

Keywords

Case report, GPIBD, HPMRS1, PIGV, facial dysmorphism, MDS

SESSION 9 – UNKNOWNS

14:45 9-YEARS OLD GIRL WITH SHORT STATURE, CONGENITAL HEART DEFECT AND DYSMORPHIC FACIAL FEATURES (UNKNOWN CASE)

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A 9-month-old girl was referred to our genetic clinic due to low birth weight, heart defect (VSD, PDA) and dysmorphic features. She was born at 39 weeks gestation with a birth weight: 2640g (small for gestational age, SGA), length: 51cm, head circumference: 32 cm; 8 points in Apgar scale. Family history regarding congenital defects and genetically related illnesses was negative.

Both motor and speech development were delayed. Currently, she is less mobile than her peers. She struggles with concentration and often forgets what she has learned. She receives support form a teaching assistant.

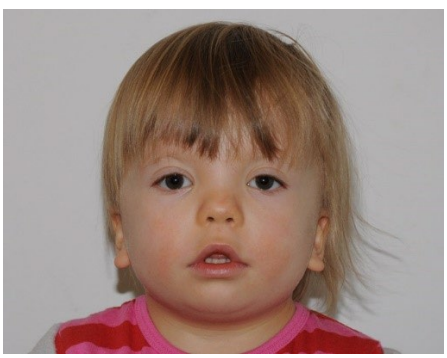
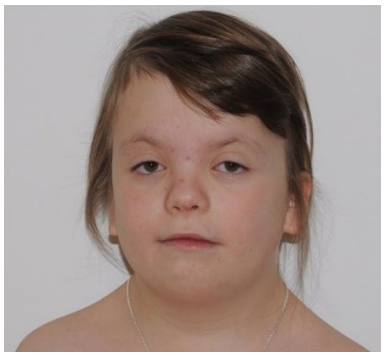
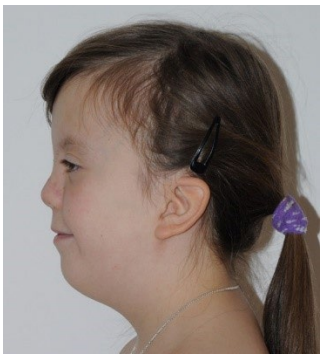
In the transfontanel ultrasound, intraventricular hemorrhage I/II was observed, and in the abdominal ultrasound, dilatation of the right renal pelvis was noted. For a period of time, the girl required catheterization due to bladder dysfunction.

Current growth parameters: height 124.2 cm (-2.27 SD), weight 26.5 kg (-0.99 SD) and head circumference 52 cm (-0.56 SD).

HPO dysmorphic features: highly arched eyebrow (HP:0002553), epicanthus (HP:0000286), ptosis (HP:0000508), low-set, posteriorly rotated ears (HP:0000368), broad neck (HP:0000475), flat face (HP:0012368), brachycephaly (HP:0000248), short nose (HP:0003196), sparse hair (HP:0008070).

Performed genetic tests: karyotype, subtelomeric test, array CGH (8x60K, Agilent Technologies) and targeted NGS panel for RASopathies (*SPRED2* not included).

Any suggestions would be greatly appreciated.

22 months **9 years**

14:57 FAMILIAL KCNMA1: IS IT THE CAUSATIVE AGENT?

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Mutations in the gene *KCNMA1* are responsible of a vast spectrum of clinical manifestations with four cardinal dysfunctions: epilepsy, movement disorders, neurodevelopmental delay and intellectual disability, malformations. Data on patients and animal models carried out in the last decade, have delineated different phenotypical patterns for gain-of-function and loss-of-function mutations. We therefore report the case of a girl who was referred to our clinic at 3 years and 5 months because of psychomotor delay, gait disturbances, failure to thrive and facial dysmorphic features. Brain MRI and EEG were normal. CMA analysis uncovered a duplication of 663.5Kb on the short arm of chromosome 9, maternally inherited. Literature review in this regard was uninformative. Subsequently, exome sequencing revealed a frameshift variant in KCNMA1 (NM_001161352.2:c.2173del p.(Ser725Glnfs*61)). This substitution is reported in a single individual in the database GnomAD v4.1 absent in the gnomAD v3.1.2 (non-neuro), but no health status information of this subject is available. The variant was thence classified as likely pathogenic according to ACMG classification criteria (PM2, PVS1). The subsequent segregation study, revealed the presence of the mutation in the mother of our patient who required educational support, reported epileptic episodes during infancy and displays similar facial features. Truncating variations in this gene are described in the literature either with gain-of-function, or loss-of-function effects, occasionally resulting in hypomorphic alleles. Based solely on the clinical picture of our patient and her mother, is not possible to determine the functional impact of the variant on the resulting protein. Additional studies are required to determine the pathogenicity of the p.(Ser725Glnfs*61) variant and to infer the possible molecular mechanisms underlying the phenotype. This

reports aims to contribute in the casuistry of KCNMA1-associated conditions, expanding the knowledge on possible genotype-phenotype correlations.

15:09 AN UNDIAGNOSED PATIENT WITH DISPROPORTIONATE SHORT STATURE, COARSE FACIAL FEATURES, CALCIFICATION OF CARTILAGE, TRACHEAL STENOSIS, CHRONIC OTITIS MEDIA, AND ECTODERMAL DYSPLASIA

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We present a 22-year-old female patient with disproportionate short stature, coarse and dysmorphic facial features, calcification of cartilage, tracheal stenosis, chronic otitis media, and ectodermal dysplasia findings.

She was born to consanguineous, healthy parents of Syrian origin. The medical history of the parents and three healthy siblings was uneventful. Prenatal follow-up, conducted in Syria, were not accessible. Her birth was at term with normal spontaneous vaginal delivery and newborn screenings were normal. She had normal intellectual development and continued her undergraduate education. She underwent an operation for chronic otitis media with cholesteatoma and intraoperative tracheotomy due to subglottic tracheal stenosis. Additionally, she had sparse hair since early childhood, black discoloration of teeth, and multiple caries, requiring implant restoration of all her teeth at age 20. She had a -2 diopter myopia and sensorineural hearing loss.

The patient's body weight was 39 kg (-3.8 SD), height was 145 cm (-3.08 SD), arm span was 136 cm (-4.62 SD), and head circumference was 52 cm (-3.32 SD). Her sitting height and all limb segments were short. Coarse facial features were noted, including prominent eyes, full cheeks, a bulbous nasal tip, thick nasal alae, a long philtrum, and full lips. Additionally, Widow’s peak, downslanted palpebral fissures, flat nasal bridge, posteriorly rotated ears, short nose, anteverted nares, retrognathia, pectoral asymmetry, scoliosis, and brachydactyly were identified. Moreover, patchy alopecia with coarse hair, acne vulgaris on the face, dry skin, plantar hyperkeratosis, and hypoplasia of the fifth toenail on both feet were noted.

The skeletal survey revealed thoracic scoliosis, brachymetaphalangy, and metatarsus adductus. CT imaging showed otitis media in the left ear, and narrowing of the air passage from subglottic to laryngeal level. Additionally, multiple calcifications were identified in various locations including the right vertex inner table, right nasal cavity, paratracheal region, outer ear cartilage, costal cartilage, trachea, and bronchi. Transthoracic echocardiography and abdominal ultrasound were normal. Basic biochemistry, including calcium, phosphorus, and alkaline phosphatase levels, and complete blood count were also normal. Gingival histopathological evaluation did not reveal any deposition, such as hyaline substance.

Although the findings suggested Keutel syndrome, some ectodermal and coarse facial features did not fit the diagnosis. We also considered GAPO syndrome, RASopathies, MACS syndrome, etc., in the differential diagnosis. Additionally, due to the multisystemic problems, we reviewed the possibility of a merged phenotype of multilocus genotype. Clinical ES analysis conducted to evaluate the etiology did not detect any variants of clinical significance.

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

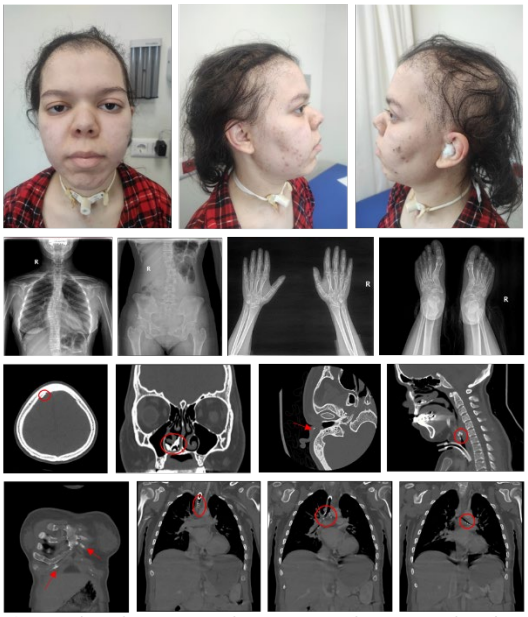

Figure: Clinical pictures and imagings. Red arrows and circles indicate calcification.

15:21 PATIENT WITH DISTINCT DYSMORPHY AND LIMB DEFECT – DOES A DIAGNOSIS OF AMNIOTIC BAND SEQUENCE FULLY EXPLAIN THE PHENOTYPE?

Monika KOWALCZYK[1], Dorota WICHER[1]

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Here we present a 12-months old boy with congenital limb defects and distinct dysmorphic features.

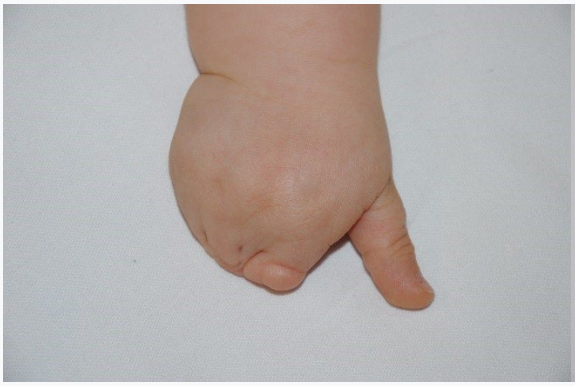
The patient was born to healthy non-consanguineous parents at 34 weeks of gestation G3 by spontaneous delivery, weight 2160g/OFC 30cm, 10 Apgar points. In mother – G1-anembronic pregnancy, G2-healthy sister. G3 was complicated by subchorionic hematoma (1st and 2st trimester) and maternal COVID infection (3rd trimester).

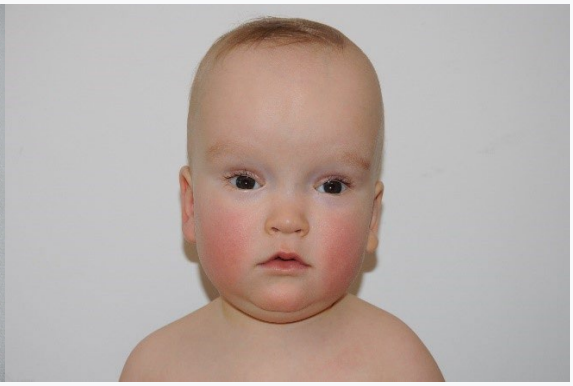
After birth malformation of upper and lower limb, clinically diagnosed as constriction rings syndrome, along with dysmorphic features, were noted. Transfontanel sonography showed caudato-thalamic groove cyst (10x10x7mm), patient is waiting for brain MRI. Constriction of lower limbs were treated by Z-plasty of the skin. His psychomotor development remains normal. The older sister presents very similar dysmorphic features, but without limb defect.

The patient's dysmorphic features include: relative macrocephaly (90th percentile, height 25-50th percentile), sparse scalp hair, large anterior fontanelle (4x3,5cm), frontal bossing, high forehead, upslanting palpebral fissures, epicanthus, low seat ears. Limb malformations include right hand syndactyly od II-V digits with their hypoplasia, left hand syndactyly of III-IV digits with hypoplasia, right clubfoot, lower limbs with scars (after surgery).

Molecular diagnostic included comparative genomic hybrydyzation and whole exome sequencing – revealed no abnormalities.

Our preliminary diagnosis is amniotic band sequence and familiar dysmorphic features. Do you agree? Do you concur or do you suggest considering another diagnosis?





16:20 A DLG4 VARIANT SEGREGATING IN A FAMILY WITH INHERITED INTELLECTUAL DISABILITY

Maria Chiara BARONI[1,2], Sien VAN DAELE[1], Gitte FLORUS[1], Kris VAN DEN BOGAERT[1], Hilde PEETERS[1]

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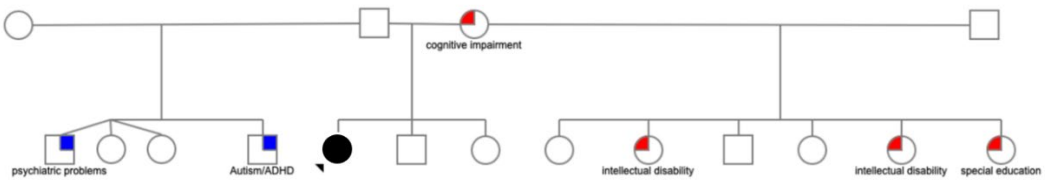
De novo variants represent the main genetic cause of Neurodevelopmental Disorders (NDD), followed by X-linked and autosomal recessive inheritance; however, over 50% of the NDD cases remain unsolved. Inherited variants with reduced disease penetrance and variable expressivity may explain some of these unsolved cases.

We present the case of a 5-year-old girl who came to our attention due to global developmental delay, behavioural abnormalities and subtle dysmorphic features. She is the first child of non-consanguineous parents and has two healthy siblings. Her mother has six children from a previous relationship: two daughters have intellectual disability and a third daughter attended special education. The mother herself was reported to have some cognitive impairment. On the paternal side, there was a family history of autism/ADHD.



The conventional karyotype and chromosomal microarray, previously performed in our proband, were unremarkable. Trio-WES analysis, requested after the genetic consultation, did not disclose causative *de novo* or biallelic variants. Given the family history on the maternal side, duo analysis with the mother was performed and detected a shared missense variant in the *DLG4* gene (NM_001365.4).

DLG4 belongs to the discs large (DLG) subfamily of the membrane-associated guanylate kinases. *DLG4*-related synaptopathy (MIM #618793) is a rare disorder characterized by developmental delay, intellectual disability (most commonly mild-to-moderate), and autism spectrum disorder. Most of the variants are loss of function and occur *de novo*. Only two cases of inherited variants have been described in the literature (Rodríguez-Palmero A. 2021, Kassabian B. 2024), with little information on the carrier parent; it should be noted that both variants were missense, located in functional domains and maternally inherited.

The variant c.1822C>G p.(His608Asp) is absent in gnomAD and is localised in the Guanylate kinase-like domain; it is not reported in the literature and is classified as VOUS according to the ACMG guidelines. Segregation analyses will be performed to evaluate carriership of the familial variant in the other affected daughters, which can provide additional evidence for pathogenicity.

In conclusion, we provide a detailed description of a family with a *DLG4* inherited variant. Our case highlights the importance of family history collection and suggests that inherited variants should be analysed in next-generation sequencing data. Further re-analysis of NGS negative samples is planned to disclose more cases of inherited NDDs.

16:30 FIRST REPORT OF A MISSENSE SATB2 VARIANT SEGREGATING IN A FAMILY

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The SATB2 gene, involved in chromatin remodeling and transcriptional regulation, is located in the 2q33.1 region, commonly associated to Glass Syndrome (MIM #612313). While this designation was originally limited to patients with chromosomal rearrangements, point mutations have been subsequently reported and included in the so-called SATB2-associated syndrome (SAS). The main features are developmental delay/intellectual disability with absent or limited speech development, craniofacial abnormalities including palatal and dental abnormalities, behavioral problems, skeletal anomalies and osteopenia.
More than 80 SAS patients have been reported in literature, mostly in the pediatric age and with de novo variants, except for two cases of mosaicism in the unaffected parent.
A 24-years-old man was referred to our Medical Genetics Unit for moderate intellectual disability, particularly affecting speech, tall stature, mild facial dysmorphisms, pectus excavatum and arachnodactyly. Clinical diagnosis of Marfan syndrome was excluded, since most family members were tall and systemic score was low. In the same session, we evaluated the 23-years-old sister, 170 cm tall, affected by moderate intellectual disability, herniated discs, mild dysmorphisms, recurrent headaches, neuropathic and osteoarticular pain. The 43-years-old mother, 178 cm tall, showed a more dysmorphic appearance, moderate intellectual disability and missing teeth. The father, described as taller than 190 cm, was not available.
We first performed SNP-array and *FMR1* analysis, with normal results. The affected trio was then tested with a clinical exome focused on intellectual disabilities. No clearly pathogenic variants were found, but a novel heterozygous missense variant – c.1553G>T p.(Cys518Phe) – in *SATB2* was found in all three individuals. The variant is extremely rare (absent in GnomAD) and is predicted as deleterious by most consulted tools. It's located in the CUT2 domain of the protein, which was already investigated in a functional study focused on similar missense variants, which were proved to alter the protein interaction with chromatin leading to complete loss of function. Adding the cosegregation ACMG criteria (PP1), the variant was then considered Likely Pathogenic.
As far as we know, this is the first report of a *SATB2* point mutation segregating in a family. The neuropsychiatric features are consistent with the disease, and pectus excavatum and arachnodactyly are also frequently reported. SAS does not usually enter in differential diagnosis with Marfan syndrome, since most SAS patients are short: in this case, tall stature was misleading. Palatal abnormalities were also absent: *SATB2* was originally described as potential cause of isolated cleft palate, but in reality less than 50% of SAS patients show palatal signs, mostly with chromosomal rearrangements. Given the risk of osteopenia, DEXA was recommended, especially in the young female affected by vertebral issues.

16:40 NEURODEVELOPMENTAL DISORDER CAUSED BY NOVEL FRAMESHIFT VARIANT IN BCL11B GENE: CASE REPORT

Rasa TRABERG[1,2], Inga NASVYTIENĖ[1], Kristina ALEKNAVIČIENĖ[1,2], Rimvydas JONIKAS[1], Rasa UGENSKIENĖ[1,2]

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Background: BCL11B is a zinc finger protein transcription factor with multiple functions in the development of the immune and nervous cutaneous systems. Recent studies in BCL11B variant patients have presented an immunophenotype, a developmental delay, and other clinical features, such as abnormal facial appearance and dental anomalies. Some patients present with immunodeficiency.

Case report: we report 8 years old male who was referred to the clinical geneticist due to developmental delay. He is first kid of unrelated Lithuanian family and he was born full term from uneventfull pregnancy. Early motor development was normal. Whiever, developmental dealy was noticed from 18 – 24 months of age with significant langue delay. The boy had only several words at age of 7 years. The boy is also very active on supervision for attention-deficit/hyperactivity disorder (ADHD). Congenital anodontia also was diagnosed. The mother did not refer ay frequent infections, any autoimmune or allergies. Dysmorphic features was noticed: microcephaly, short palpebral fissures, hyperthelorism, narrow nasal bridge, microstomia and small jaw.

Genetic testing: whole exome sequencing showed likely pathogenic heterozygous variant in BCL11B gene NM_138576.4:c.[1988del];[1988=] that case frameshift p.([Glu663GlyfsTer60)];[(Glu663=]).

Discussion: The diagnosis of Intellectual developmental disorder with dysmorphic facies, speech delay, and T-cell abnormalities, MIM# 618092 was confirmed. Less than 50 patient is reported in the literature and found variants were missense variants, splice variant, and most frequently truncated variants. Patients with missense variants tend to have a more severe immunodeficiency, which may be due to the loss of DNA binding.

Conclusions: we report novel BCL11B gene variant that cause neurodevelopmental disorder. Future studies (eg. methylation analysis) to confirm pathogenicity of the variant is needed.

16:50 THE LONG JOURNEY TO AN ULTRA-RARE DISEASE: A CASE WITH RARB MUTATION

Şule Altıner[1], Mustafa Oğuz Acar[1], Halil Gürhan Karabulut[1]
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Syndromic microphthalmia 12 (OMIM#615524) is an ultra-rare disorder that 20 cases have been reported to date. Heterozygous *de novo* gain-of-function missense variants and bi-allelic loss-of-function variants in retinoic acid receptor beta *(RARB)* gene are associated with this syndrome. The *RARB* gene is a vitamin A-dependent retinoic acid receptor and has important roles in cell differentiation, proliferation, and

organogenesis. Retinoic acid signaling plays a key role in the development of neuroectoderm, foregut endoderm and trunk mesoderm and contribute development of eye in mammals. Syndromic microphthalmia 12 is a developmental disorder characterized by eye malformations and variable involvement of other organs. In addition to microphthalmia, the most reported findings are developmental delay, heart defects, and spasticity. Patients have clinical findings that concern various systems, as well.

The female patient, who was evaluated in our clinic at the age of 1, had bilateral microphthalmia, corneal opacity, microcephaly, anal stenosis, rectovaginal fistula, wide ascending aorta, persistent superior vena cava, high left hemidiaphragm, arachnoid cyst, mega cisterna magna, reflux, and chronic malnutrition. The patient, was born at term 3300 grams, was the second child of non-consanguineous the parents and there was no significant medical history in the family. During follow-ups, microdontia, spasticity and epilepsy are added to the patient's findings.

Over the following years, a series of genetic tests are performed for various prediagnoses. Karyotyping, 22q11.2 FISH, microarray, and sequence analysis of *BCOR, FOXC1, PITX2* genes were normal.

In the whole exome sequencing analysis performed at the age of 10 years old, a heterozygous *RARB*, NM_000965.5, c.1159C>T (p.R387C) mutation was detected and the patient diagnosed with syndromic microphthalmia 12. By segregation analysis, the mutation was determined to be *de novo*. Genetic counseling was given to the family regarding the disease. Due to severe spasticity cases reported after the genetic diagnosis, the patient started receiving appropriate physical therapy.

Making a genetic diagnosis appropriate to patients' clinics is very important in terms of patient follow-up and genetic counseling. Although it varies depending on the diagnostic tool used, the average time to receive an accurate diagnosis of a rare disease is 4-5 years. Since ultra-rare diseases are less known, the diagnosis process is more difficult and takes longer time. Almost half of the cases reported in the literature of syndromic microphthalmia 12, which causes severe symptoms from prenatal period, were diagnosed after the age of five. With this case, we aimed to share the 10-year diagnosis process of an ultra-rare patient and to contribute to making this disease more known by presenting it.

17:00 ADDING PIECES TO THE PUZZLE: SUBTLE DYSMORPHIC TRAITS IN ASSOCIATION WITH A NOVEL NCKAP1 VARIANT

Ozge Beyza Gundogdu Ogutlu[1], Berrin Demir[2], Zeynep Utlu[3], Merve Karabak[4], Oguzhan Yaralı[1]

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[2]Department of Radiology, Erzurum City Hospital, Erzurum, Turkiye
[3]Atatürk University, Department of Skin and Venereal Diseases, Erzurum, Turkiye
[4]Erzurum City Hospital, Department of child and adolescent psychiatry, Erzurum, Turkiye

Background: The *NCKAP1* gene's association with neurodevelopmental disorders (NDDs) presenting with autism spectrum disorder (ASD) traits is understudied, with no related disorder cataloged in the OMIM database. We present a pediatric case exhibiting a spectrum of NDD features and subtle dysmorphic traits associated with a novel de novo NCKAP1 variant, underscoring the importance of documenting such features to enrich phenotypic profiling (1).

Case Presentation: The infant, born at 27 weeks of gestation, faced significant initial challenges requiring intensive neonatal care. Developmental trajectories were marked by speech regression and motor delays, with seizure onset at three months. Remarkably, the patient demonstrated speech recovery following a seizure-free interval. Behavioral evaluation noted patterns of self-harm, social disengagement, and disrupted sleep. Notably, the patient displayed subtle dysmorphic features, including microcephaly, a posteriorly positioned hairline, broad eyebrow ridge, sparse eyebrows, a prominent forehead, and fusiform fingers, enriching the phenotype spectrum for NCKAP1-related disorders.

Genetic Findings: Genetic testing revealed a *NCKAP1* (NM_013436.5) c.2021+1G>A *de novo* variant within the *NCKAP1* gene, contributing to the limited pool of known cases. This variant adds to the understanding of the gene's impact on neurodevelopment, particularly as it relates to nuanced dysmorphic presentations.

Conclusions: Although subtle, the dysmorphic features in this case of an NCKAP1 variant contribute valuable information to the phenotype spectrum, suggesting a broader clinical presentation than currently recognized. This case emphasizes the importance of nuanced phenotypic descriptions in genetic disorders with few reported cases, underscoring the need for further research and detailed case reporting to inform clinical practice and management.

References:

(1)Guo, H., Zhang, Q., Dai, R., Yu, B., Hoekzema, K., Tan, J., ... & Xia, K. (2020). NCKAP1 disruptive variants lead to a neurodevelopmental disorder with core features of autism. *The American Journal of Human Genetics*, *107*(5), 963-976.

17:10 EVOLUTION OVER TIME OF A ATP6V1A RELATED DISORDER: EXPANDING THE MILDER END OF THE SPECTRUM

Simone Carbonera[1], Thomas Foiadelli[2], Ivan Taietti[2], Myriam Donesana[2], Francesco Bassanese[2], Andrea Martina Clemente[2], Eliana Barbato[2], Alessandro Orsini[3], Alessandro Ferretti[4], Salvatore Savasta[5], Silvia Kalantari[1], Fabio Sirchia[1,6]

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[3]Pediatric Neurology, Azienda Ospedaliero-Universitaria Pisana, Pisa University Hospital, Pisa, Italy
[4]Department of Neurosciences, Mental Health and Sensory Organs (NESMOS), Faculty of Medicine and Psychology, Pediatric Unit, Sapienza University of Rome, Sant'Andrea University Hospital, Rome, Italy
[5]Pediatric and Rare Diseases Clinic, Ospedale Microcitemico, Cagliari, Italy
[6]Medical Genetics Unit, Department of Diagnostic Medicine, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

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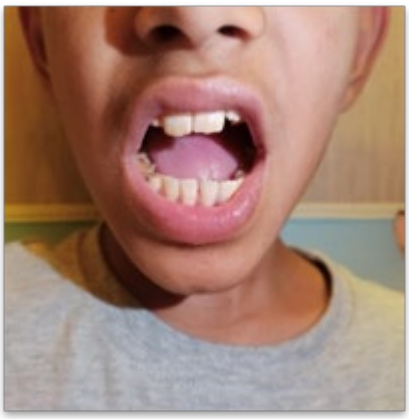
Developmental and epileptic encephalopathy 93 (#OMIM 618012) is a relatively new disorder of lysosomal homeostasis, having been described for the first time by Fassio et al. in 2018. It is caused by heterozygous variants falling in the *ATP6V1A* gene on chromosome 3, which result in neurologic manifestations ranging from early lethal epileptic encephalopathy to mild intellectual disability. Epilepsy is the most defining feature, being present in up to 80% of patients, and it is paralleled by MRI findings of hypomyelination and

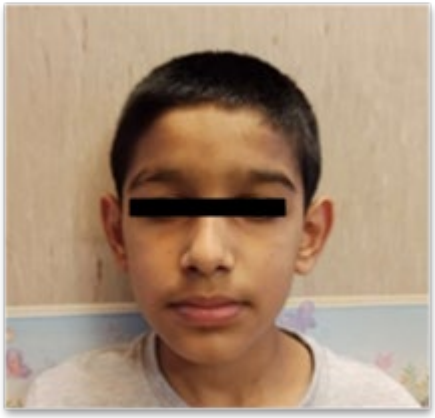
atrophy. Both these findings and the intellectual disability are progressive in most cases. Other features include early hypotonia, microcephaly and, characteristically, enamel dysplasia.

We report the case of a male patient with mild intellectual disability and speech delay manifested at age 6. He also presented microcephaly and enamel dysplasia. Whole exome sequencing was performed, allowing the identification of a *de novo* heterozygous variant in *ATP6V1A* c.82G>A p.(Val28Met). The variant is currently undescribed and is classified as likely pathogenic (PP3, PM2). Although the patient presented two episodes of seizures during fever, he currently has not developed epilepsy at 12 years of age. Notably, MRI scans performed at presentation and at age 11 did not show the usual pathologic signs. Furthermore, the patient showed signs of improvement during follow-up, in contrast to the usually progressive nature of the disorder.

In conclusion, we report a novel pathogenic *ATP6V1A* variant in a patient with unusual presentation being monitored over time, expanding the less severe end of the disorder phenotypical spectrum. Our findings provide further evidence for the need to look for *ATP6V1A* variants in patients with intellectual disability even without epilepsy, especially when enamel dysplasia is present.



1 - Patient lacking notable dysmorphic features



2 - Enamel dysplasia

17:20 EPISIGNATURE AS A DIAGNOSTIC TOOL IN A CASE OF WIEDEMANN-STEINER SYNDROME

Adelaide Peruzzi[1,2], Marco Ferilli[3], Cecilia Mancini[3], Camilla Cappelletti[3], Irene Ambrosetti[1,2], Isabelle Bacchi[1,2], Roberta Zuntini[1], Stefano Caraffi[1], Alessandra Terracciano[4], Francesca Clementina Radio[3], Andrea Ciolfi[3], Antonio Novelli[4], Marco Tartaglia[3*], Livia Garavelli[1*]

1 Medical Genetics Unit, Azienda USL-IRCCS di Reggio Emilia, 42123 Reggio Emilia, Italy
2 Department of Medical and Surgical Science, Postgraduate School of Medical Genetics, Alma Mater Studiorum University of Bologna, 40126 Bologna, Italy.
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**These authors coordinated this work.*

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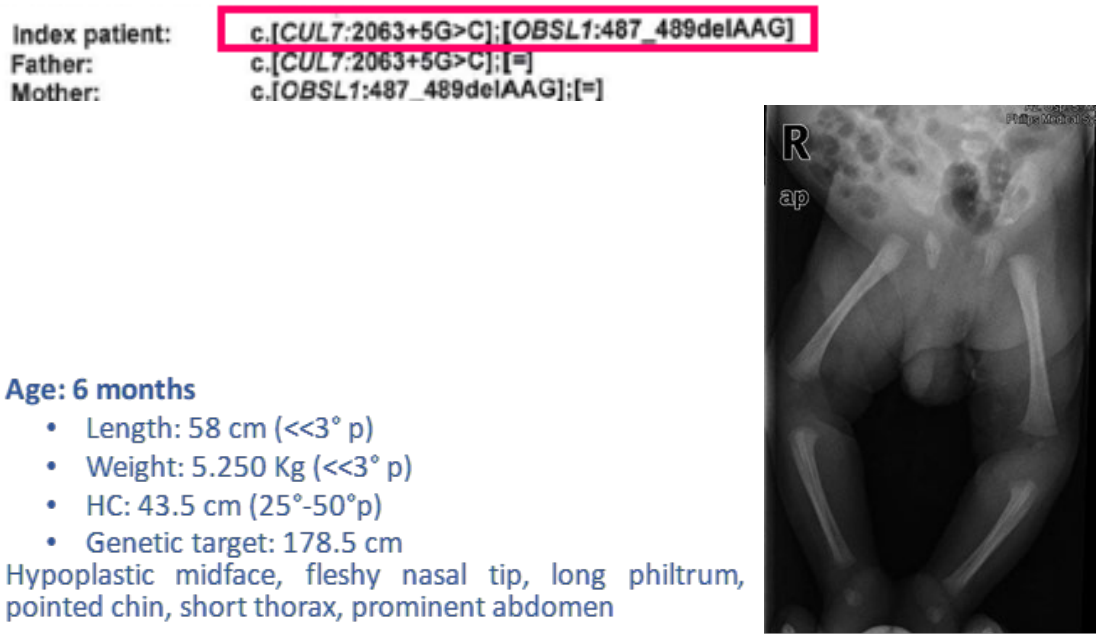
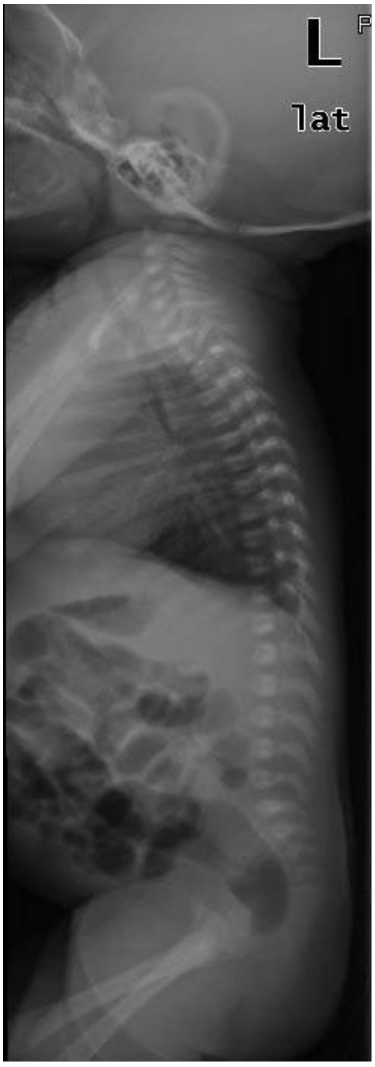
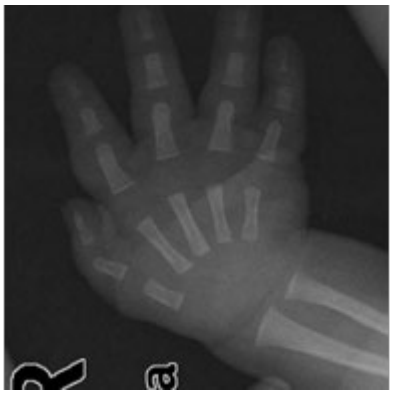
Clinical case We describe the detailed clinical evolution of a 18-years-old girl, second child of unrelated parents. Generalized hypertrichosis and intestinal subocclusion were present at birth. Feeding difficulties, recurrent vomiting and poor weight gain characterized the first year of life. A slightly delayed psychomotor development, mild intellectual disability (Leiter-R: QIT 68), benign occipital epilepsy, strabismus, overweight, polycystic ovary, cervical vertebral anomaly, chronic constipation, and recurrent respiratory infections are the main clinical features of the following years.

Physical exam At our last examination, at 18 years old, height was 156 cm (10^{th} centile), weight 69 kg (90^{th} centile), OCF 54.5 cm (50^{th}-75^{th} centile). BMI: 28.4 Kg/m2 Pubertal stages: A++P4B4, Menarche at 15 years. The patient's facial features included high forehead, arched eyebrows, hypertelorism, long eyelashes, upslanted and slightly vertically narrowed eyes, rounded and bulbous nasal tip, large columella, broad philtrum, fleshy lips, slight retrognathia, small teeth, high palate, generalized hypertrichosis of face, upper limbs, elbows, lower and back.

Investigations Due to the distinctive clinical findings, Wiedemann-Steiner syndrome (WDSTS) was suspected. Since CGH array and clinical exome sequencing yielded negative results, genome-wide DNA methylation profiling (EPIC) of the proband was performed, documenting a pattern fitting the DNA methylation signature previously associated with loss-of-function *KMT2A* variants. Based on these findings, a re-analysis of the exome sequencing data and functional validation are ongoing.







Thin bones
Diaphyseal constriction
Cortical thickening
High vertebrae

Age: 2 years Height: 77 cm (<<3° p)

- Weight: 8.150 Kg (<<3° p)
- HC: 50 cm (25°-50°p)

But no one has ever demonstrated digenic inheritance in 3M s.

First step in 2012: *CUL7* and *OBSL1* Sequencing

3M syndrome

17:30 PRESENTATION OF ADULT-ONSET ISOLATED HYPERTROPHIC CARDIOMYOPATHY WITH HOMOZYGOUS LZTR1 VARIANT: A CASE REPORT

Abdullah Sezer[1], Fatma Zehra Yalçın[1], Özge Kurmuş Ferik[2], Sinan Boz[2]

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2.Department of Cardiology, Etlik City Hospital, Ankara, Turkey

Noonan syndrome (NS; OMIM 163950), a RASopathy, is a clinically variable disorder characterized by congenital heart disease, hypertrophic cardiomyopathy (HCP), reduced postnatal growth, facial

dysmorphism, skeletal, hematological, lymphatic anomalies, variable cognitive deficits and susceptibility to certain cancers. NS occurs in approximately 1 in 1000 to 1 in 2500 individuals. This syndrome is genetically heterogeneous and is usually inherited as a dominant trait. More recently, the use of hypothesis-free approaches has allowed the discovery of novel NS disease genes, including zipper-like transcriptional regulator 1 (*LZTR1*). The *LZTR1* gene encodes a signal transducer or modulator that does not belong to the 'classical' RAS-MAPK signaling backbone, and its function in RAS signaling is unclear or poorly characterized. Pathogenic variants in the *LZTR1* gene have been shown to cause NS phenotype with both autosomal recessive and autosomal dominant inheritance, as well as adult-onset predisposition to schwannomatosis. In this report, we aim to present a patient with a homozygous missense variant in the *LZTR1* gene who did not exhibit classical findings of the NS phenotype except for HCP.

The 38-year-old patient was the 2nd child of healthy consanguineous parents. The patient was diagnosed with HCP, presenting with complaints of palpitation and weakness for several months. The patient did not have a history of heart disease or surgery during childhood. His neurological development, growth, and school performance were normal. ECG and holter monitoring showed normal sinus rhythm with no rhythm disorder, and echocardiography and cardiac MRI were compatible with HCP. The patient did not have characteristic findings or typical dysmorphic features seen in Noonan syndrome. His height and weight were normal. His 42-year-old brother was also clinically diagnosed with HCP, but he could not be evaluated in our outpatient clinic. Clinical exome sequencing analysis of the proband revealed a homozygous likely pathogenic variant, c.2387T>C p.(Ile796Thr), in the *LZTR1* gene (NM_006767). This variant has been previously reported in NS patients with autosomal recessive inheritance.

Biallelic variants in the *LZTR1* gene were first reported in patients with an early-onset typical NS phenotype, characterized by cardiac problems, dysmorphic facial features, and short stature. Some later reports also describe patients with a nonsyndromic presentation, where only cardiac involvement is present. In the literature, at least one additional case has been reported with late-onset presentation solely with HCP, similar to the case presented here. Adult-onset isolated HCP presentation may be due to the phenotypic variability of the disease or may represent a new clinical entity associated with *LZTR1*. Further patient reports and additional studies are needed to clarify this situation.

17:40 FINDING LIGHT IN THE DARKNESS: IDENTIFICATION OF AN ARID1A INTRONIC DELETION IN COFFIN-SIRIS-SYNDROME

Sarah SCHUHMANN[1], Georgia VASILEIOU[1,2], Steffen UEBE[1], Andreas FINK[1], Antje WIESENER[1], Marielle ALDERS[3], Jennifer KERKHOF[4], Bekim SADIKOVIC[4,5], Bavarian Genomes Network, André REIS[1,2]

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Disruption of chromatin regulatory genes belonging to the BAF complex represents one of the most frequent genetic cause for neurodevelopmental disorders (NDD). Coffin-Siris syndrome (CSS) is a multiple congenital anomalies NDD caused by pathogenic variants in 11 different BAF complex genes. However, in a subset of cases with a suspected CSS diagnosis the genetic basis remains unsolved.

Within the research project *Bavarian Genomes Network* we identified a four year old female individual from healthy non-consanguineous parents with global neurodevelopmental delay, muscular hypotonia, hypoplasia of the corpus callosum, coarse facial features, sparse scalp hair, hypoplastic toe nails, laryngotracheomalazia and dysplastic aortic valve suggestive of CSS. As trio exome sequencing and CNV analysis did not identify a causative variant, we applied short-read genome sequencing (GS).

Trio GS revealed a *de novo* 24 kb deletion located in intron 4 of the *ARID1A* gene, which is associated with CSS type 2. To better characterize the effect of the deletion we applied further genomic assays. RNA sequencing showed a 166 bp intron retention in 24% of the reads, predicted to result in the formation of a toxic exon and a frameshift with premature termination codon after 9 amino acids. This represents a loss-of-function allele compatible with the clinical diagnosis of CSS type 2. Methylome analyses confirmed a BAFopathy episignature in this individual.

To our knowledge this case represents the first intronic deletion identified in a patient with ARID1A associated CSS. Our case highlights the benefits of GS in the diagnosis of unsolved cases as well as the necessity of additional genomic techniques to interpret variants in non-coding regions.

Saturday 21st of September

SESSION 11 – DUAL DIAGNOSIS

09:00 THE ROUTINE APPLICATION OF TRIO DIAGNOSTIC GENOME SEQUENCING FOR PATIENTS WITH AN UNCERTAIN PHENOTYPE DIAGNOSIS IS THE ROBERT DEBRE GENETIC DEPARTMENT'S EXPERIENCE

Alain Verloes, Yline Capri, Laurence Perrin, Xenia Latypova, Antoine Pouzet, Lyse Ruaud, Emilie Serrano, Jonathan Lévy, Nathalie Couque, Yoann Vial, Corinne Collet, Séverine Drunat and the network of molecular biologist of SeqOIA Laboratory (head: Pierre Blanc)

Genetic Department, APHP-Robert DEBRE university hospital and SeqOIA laboratory, APHP hôpital Broussais Hospital, Paris, France and ERN-ITHACA

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Since 2022, a programme initiated by the French Ministry of Health has made it possible to offer a trio genome study as part of routine care in the frame of the Fourth National Rare Disease Plan. Analyses are carried out on clinical preindications (> 70), and coded according to the HPO ontology.Samples are sequenced by two publicly-funded and coordinated sequencing facilities (one in Paris, for the North and West of France, and the other in Lyon), each with its own team of bioinformaticians. Genomic analysis is carried out by a network of accredited molecular biologists working in most of the country's university hospital genetic labs, which are acknowledged for their expertise in one or several gene panels. Only class 4 or 5 results, and some class “3+” results, are returned after validation in a multidisciplinary

clinicobiological consensus conference. Secondary data are not reported. Sequences are stored in a national health data warehouse and are available for research. The current turnover is around five months.

Between 2022 and May 2024, our department prescribed almost one thousand of trios in the context of developmental anomalies or neurodevelopmental disorders when the clinical diagnosis was not obvious. No preliminary investigation was required (fragile X in parallel if clinically relevant). By mid-May 2024, we had the result for 656 patients, most of them analysed in trio. We obtained a convincing molecular diagnosis in 316 patients (48%): 293 patients (94% of affected patients), carried at least pathogenic variant(s) in one among 262 genes. 34 patients (11%) had a chromosomal rearrangement. Among those, eleven patients combined a chromosomal anomaly and one monogenic anomaly. In our "genetic" group, 265 patients had pathogenic variants in one gene (92%), 24 in two genes, and two in three genes. We will illustrate some of these patients with double or triple hits, resulting in a hybrid phenotype (a source of clinical error in interpretation) or a cumulative phenotype (addition of several genes responsible for ID). By reevaluating the series in june 24, we further identified 6 patients with pathogenic RNU4.2 variants (confirmation pending).

Our results demonstrate the clear benefits of genome sequencing as a first-tier approach in routine, outperforming exome sequencing in many cases, and the efficiency of a centralized wet lab.

09:10 A PATIENT WITH NEUROFIBROMATOSIS 1 AND SIFRIM-HITZ-WEISS SYNDROME WITH DEXTROCARDIA

Tarik Duzenli[1], Serdar Mermer[2], Gülsüm Kayhan[1]

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Introduction: Sifrim-Hitz-Weiss syndrome (SIHIWES; OMIM #603277) is a rare neurodevelopmental disorder caused by heterozygous pathogenic variants in the chromodomain helicase DNA-binding protein 4 (*CHD4*) gene. This syndrome is characterized by developmental delay/intellectual disability, congenital heart defects, brain abnormalities, ophthalmological abnormalities, hearing impairment, and skeletal/limb abnormalities. Neurofibromatosis 1 (NF1; OMIM # 613113) is a well-known multisystem disorder caused by heterozygous pathogenic variants in the neurofibromin (*NF1*) gene with a prevalence of 1 in 3,000 to 1 in 4,000 individuals. In this report, we present a patient with a dual phenotype of SIHIWES and NF1.

Case report: A 6-month-old male patient was referred to our clinic for evaluation due to dysmorphic appearance, dextrocardia, bilateral postaxial polydactyly, hydrocephalus, and multiple café au lait macules. He could control his head at four months, but other developmental milestones weren't reached. His dysmorphic facial features are a broad forehead, frontal bossing, hypertelorism, a short nose, a thin upper lip, posteriorly rotated ears, bilateral postaxial polydactyly of the hands and feet, and multiple café au lait. (Fig 1.) Array CGH was normal. Whole exome sequencing revealed a heterozygous likely pathogenic c.4256G>A (p.Arg1419His) variant in the *CHD4* (NM_001273.5) and a heterozygous pathogenic c.1411A>T (p.Lys471Ter) variant in the *NF1* (NM_001042492.3) gene.

Conclusions: This is the first report in the literature on the co-existence of SIHIWES and NF1. Dextrocardia is a novel finding that has not previously been reported in either syndrome. Considering the role of *CHD4* in cardiac embryology, it can be argued that it is a novel finding of SIHIWES. The addition of dextrocardia to the

previously described findings, including polydactyly and hydrocephalus, suggests that a gene related to ciliary function may be a downstream target of *CHD4*. Further clinical reports and studies are needed to elucidate the clinical characteristics of this disorder.

Figure 1: Photographs of the patient at the age of 6 months (a) and 4.5 years (b). Written informed consent was obtained from the patient's parents to publish a clinical report with photographs of the patient

09:20 DUAL DIAGNOSIS OF SOTOS SYNDROME AGGRAVATES THE CLINICAL PRESENTATION OF A YOUNG CHILD WITH RETT SYNDROME

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We describe the case of a 2 years old girl with a dual molecular diagnosis of Rett and Sotos syndrome. “Double trouble” in rare diseases is estimated to occur in up to 7% of all diagnoses, but is often difficult to recognize, especially in young children.

The proband is the third child of non-consanguineous parents of Albanian origin, with no relevant family history of disease. She was admitted to the Hospital of Parma for respiratory distress due to milk inhalation, and was fitted with a feeding tube. Severe hypotonia, abnormal EEG and secundum atrial septal defect with left-right shunt (surgically corrected at the Hospital of Bologna) were detected. WES from a buccal swab revealed a known pathogenic variant in the *MECP2* gene, NM_001110792.2:c.[799C>T];[=] / p.(Arg267*), and a likely pathogenic variant in *NSD1*, NM_022455.4:c.[5629C>T];[=] / p.(Arg1877Cys).

At 23 months 2 weeks of age she was examined at the medical genetics unit of the Hospital of Reggio Emilia. She presented with length 91 cm (95th percentile, +1.6 SD), weight 10.9 Kg (16th p, -1 SD), head circumference 46 cm (16th p, -1 SD; measurement at birth not available to evaluate head growth), and severe developmental delay. Bruxism, stereotypical hand movements and self-aggressive behavior, in the presence of eye contact, were consistent with typical Rett syndrome, but the severity of the psychomotor delay suggested a contributing role of the *NSD1* variant. Duplication of renal pelvis and cortical hyperechogenicity in the right kidney, together with the heart defect, supported the comorbidity for Sotos syndrome. Sharing of clinical information between hospitals, along with segregation analysis in the parents demonstrating a *de novo*

origin for both variants, confirmed the dual diagnosis. The *NSD1* missense variant, absent in reference population databases and occurring in a well-conserved protein domain with frequent deleterious substitutions, was reclassified as pathogenic.

This report highlights the benefit of wide-spectrum NGS analysis in infants and young children, and the importance of a tight collaboration among health services in the same territorial area.

09:30 TRIPLE DIAGNOSIS- CHALLENGES

Aleksandra PIETRZYK[1], Sabina LICHOŁAI[1], Ewa STUDNIAK[2], Anita KRAWIEC[3], Agnieszka SOBCZYŃSKA-TOMASZEWSKA[3],

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A 9-year-old patient was referred to our clinic for reconsultation due to: clinical suspicion of pseudohypoparathyroidism, presenting symptoms inexplicable with previous diagnosis of 47,XXX and intense parental anxiety. Upon examination: ataxia, dysarthria, intellectual disability, behavioral abnormalities, urticaria, tall stature, obesity, dysmorphic features were observed. Additional testing showed hypothyroidism and hypercholesterolemia. Whole exome sequencing was performed, revealing heterozygous loss of function variant in *LZTR1* gene of known pathogenicity as well as uniparental disomy of chromosome 20, which was confirmed by MLPA to be paternal in origin. Diagnosis of pseudohypoparathyroidism Ib was given and suspicion of RASopathy supported by some of clinical features observed in the patient.
The challenges encountered in this patient concern phenotyping due to overlapping features as well symptoms suppressed by coexistent diseases, further management and diagnosis prolonged by decreased alertness caused by previous diagnosis of 47,XXX.

09:40 AN UNUSUAL CO-OCCURRENCE OF BICORONAL CRANIOSYNOSTOSIS AND HYPOCHONDROPLASIA: CASE REPORT

Abdullah Sezer, Atakan Deniz, Abdülkerim Kolkıran

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Fibroblast growth factor receptors (FGFRs) are crucial in regulating cartilage cell growth and differentiation, essential for bone formation. Abnormal activation of *FGFR* genes (*FGFR1-3*) can cause developmental disorders like craniosynostosis (CRS) and skeletal dysplasia. *FGFR3*-related hypochondroplasia (HCH) is a rare genetic disease characterized by short stature, stocky build, short limbs, broad hands and feet, mild joint laxity, and a large head. Radiological findings include shortened long bones with mild metaphyseal flare, among others. The c.1620C>A/G p.(Asn540Lys) variant in *FGFR3* explains 70%-80% of HCH cases, showing specific genotype-phenotype correlations. Patients with HCH exhibit milder skeletal features than those with achondroplasia (ACH). Symptoms typically appear in toddlers or school-age children, but can also be detected prenatally or in early infancy.

A 3-month-old female presented with bicoronal CRS, syndromic facial appearance, and short stature. She was born to healthy, non-consanguineous parents at 38 weeks gestation via cesarean section, with a birth weight of 3500 grams and length of 49 cm. Her brother had agenesis of the corpus callosum (CC). Physical examination showed brachycephaly, prominent forehead, flat supraorbital margins, depressed nasal bridge, midface retrusion, rhizomelic shortening, and overlapping toes. Anthropometric measurements indicated a height of 55.5 cm (-1.93 SDS), weight of 5.6 kg (-0.39 SDS), and head circumference of 39 cm (-0.93 SDS). Imaging revealed bicoronal CRS, brachycephaly, small anterior fontanelle, herniation of cerebellar tonsils, and CC hypoplasia. Cardiac evaluation showed a small ASD and mitral regurgitation. Basic metabolic and endocrine screenings, as well as abdominal ultrasound examination, and audiological, and visual screenings were normal. The patient underwent calvarial remodeling surgery for CRS.

Although the patient's phenotype suggested an *FGFR3*-related skeletal dysplasia such as ACH and HCH, the unusual combination of CRS led us to plan a more comprehensive genetic evaluation. Clinical-exome sequencing analysis revealed only the heterozygous c.1620C>A p.(Asn540Lys) pathogenic variant in the *FGFR3* gene. Finally, the patient was diagnosed with HCH. To the best of our knowledge, the unusual combination of CRS and HCH has been reported only twice in the literature. While bicoronal CRS is typical in another *FGFR3*-related skeletal disorder, Muenke syndrome, the patient's appendicular skeletal involvement did not align with this diagnosis. Additionally, the patient's clinical severity and age-of-onset resembled ACH more than HCH. In conclusion, this case, which exhibits a phenotype different from classical HCH, can be considered a new *FGFR3*-related clinical entity, as well as a phenotypic expansion of HCH. It underscores the importance of ongoing monitoring for CRS in individuals with HCH.

09:50 A CASE WİTH CRİ-DU-CHAT SYNDROME AND GOLDENHAR SYNDROME

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Introduction: Cri-du-chat syndrome is an autosomal dominant disorder caused by deletion of the short arm of chromosome 5 and characterised by microcephaly, hypertelorism, epicanthal folds and intellectual disability. A high-pitched, cat-like cry is the most characteristic feature of the syndrome. Craniofacial microsomia (also known as Goldenhar syndrome) is an autosomal dominant disorder characterised by facial asymmetry, microtia, preauricular skin tags, lateral oral clefts, mandibular hypoplasia and cardiac anomalies such as septal defects. Here we present a 16-month-old Turkish girl with the features of both Cri-du-chat syndrome and Goldenhar syndrome.

Case Report: A newborn female patient was referred to our clinic because of dysmorphism and poor sucking. She was born at the age of 35+3 weeks to non-consanguineous healthy parents with a birth weight of 2250 gr (-2,56 SDS). She passed the newborn hearing screening and her newborn metabolic screening results were also normal. There was no relevant family history. Her physical examination revealed microcephaly, facial asymmetry, hypertelorism, epicanthal folds, depressed nasal bridge, preauricular skin tags, lateral oral cleft, microretrognathia, mandibular hypoplasia and scoliosis. Cardiac imaging showed an atrial septal defect. Her neurological examination was normal. Oesophagogastroduodenoscopy, transfontanellar ultrasound and whole abdominal ultrasound were normal. Karyotype analysis and chromosomal microarray analysis were performed.

Results: Karyotype results showed 46,XX,del(5)(p13) and microarray analysis confirmed a loss of 29Mb within the 5p15.33p13.3 chromosomal regions. Both karyotype and microarray analysis confirmed Cri-du-chat syndrome. The parents' karyotype and microarray analysis were normal, suggesting that the patient's deletion was *de novo*.

Discussion: This case is noteworthy as a rare case with features of both Cri-du-chat syndrome and craniofacial microsomia. Patients with features of both syndromes have been reported in the literature and our patient is consistent with the literature. The symptoms of craniofacial microsomia and the findings of cri-du-chat syndrome may point to candidate genes, particularly in the 5p region. The rarity and complexity of such cases calls for further research into similar cases and a better understanding of the potential relationships and interactions between the two syndromes. Further studies may help in the management of similar cases and may lead to improved patient care.

10:00 ASSOCIATION OF A MISSENSE FLT4 KINASE DOMAIN VARIANT WITH MILROY DISEASE AND CARDIAC DEFECTS

Isabelle Bacchi[1,2], Roberta Zuntini[1], Giulia Barbato[3], Francesco Leo[3], Luca Pagliai[1], Silvia Braibanti[3], Giancarlo Gargano[3], Livia Garavelli[1]

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Determining the etiology of primary lymphedema in newborns poses challenges, particularly in the absence of family history. This condition can manifest as either isolated or syndromic, with over 20 genes identified thus far in association with its presentation. Milroy disease (OMIM#153100) is an autosomal dominant condition determined by the alteration of the lymphatic system development, that leads to chronic localized swelling of body parts - in particular the lower limbs. Pathogenic variants linked to Milroy disease cluster within the kinase domain of the *FLT4* gene. We present a case of a newborn exhibiting congenital lymphedema affecting the lower limbs, genitals, and upper lip, alongside patent foramen ovale (PFO) and stenosis of the left pulmonary artery. Firstly, whole exome analysis was performed and the result was filtered for genes associated with lymphedema, revealed the variant in the *FLT4* gene (NM_182925.5):c.3122G>A p.(Arg1041Gln) (rs121909650). This variant is classified as pathogenic according to ACMG criteria and it has already been reported in the literature in patients affected by Milroy disease. To our knowledge, neither this variant nor any missense variant within *FLT4* kinase domain has previously been linked to clinical presentations encompassing both lymphedema and cardiac defects. Conversely, it is known that deleterious variants affecting the immunoglobulin domains of *FLT4* are associated with Tetralogy of Fallot, with or without other cardiac anomalies. Secondly, data exome reanalysis for genes related to cardiopathy was performed: the genetic test did not reveal pathogenic or likely pathogenic variants in these genes. This report highlights new insights useful for the genotype-phenotype correlation of pathogenic variants in *FLT4* and provides valuable information for the cardiac follow-up of patients with Milroy disease.

10:15 LONG READ WHOLE GENOME SEQUENCING IN DEVELOPMENTAL DISORDERS : ONE FITS ALL ?

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Background: The implementation of massive parallel sequencing as standard of care enabled to simplify the diagnostic odyssey of patients with developmental disorders (DD) and lead to the discovery of several new causative genes. However, several molecular causes of DD such as tandem repeat expansions and imprinting still require specific targeted assays. In many cases, further functional assessments such as X-chromosome inactivation (XCI) and episignatures are also still needed to classify identified variants. In addition, a large part of structural variants (SVs) remains inaccessible. With the advent of long-read sequencing (LRS) technologies, the detection of single nucleotide variants (SNVs), SVs and base modifications in a single assay recently became reality.

Methods: To evaluate the potential of LRS for the diagnosis of DD, we performed whole genome nanopore sequencing in 30 patients with episignature-associated disorders as well as 25 patients (and their parents) with intellectual disability and/or multiple congenital anomalies without molecular diagnosis after short read exome or genome sequencing. We developed an analytical pipeline to concomitantly assess single nucleotide, structural and epigenetic variation in a haplotype-aware manner. We evaluated the detection of episignatures using array-based reference data and explored the added diagnostic yield of LRS for DD, using both the hg38 and T2T references.

Results : Looking for hitherto unidentified causal SVs, we identified few (0.2 de novo and 1.4 X-linked SV /individual) but potential interesting de novo and X-linked SVs. Inherited variants are currently being investigated. Haplotype-aware methylation calling enabled us to detect both imprinting defects and skewed XCI. Our proof-of-concept study using array-based data as reference, showed non inferiority of LRS for episignature detection, and illustrated the concomitant assesment of both the episignatures and their underlying genomic variants.

Conclusion: LRS enables a comprehensive analysis of both genomic and epigenomic variation underlying DD. The added value of the technology will be illustrated through some interesting clinical cases. We envision that the assessment of secondary but also primary epigenetic variants will shed light on molecular causes of DD in the future.

10:30 DYSMORPHOLOGY QUIZ

Emilia K BIJLSMA[1],

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This session will present knowns, i.e. syndromes or characteristic features of known disorders. Active participation of the audience will be required.

SESSION 12 – CYTOGENETICS

11.00 JACOBSEN-SYNDROME CAUSED BY CHROMOTHRIPSIS

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Background: Jacobsen syndrome (JBS; 11q23 deletion syndrome, OMIM #147791) is a rare genetic disorder caused by a partial deletion of chromosome 11q. JBS is characterized by specific craniofacial dysmorphism, multiple congenital anomalies and skeletal abnormalities. Affected individuals typically show growth and developmental retardation as well as neurodevelopmental delay. Often, clinical features include heart defects, hypotension, thrombocytopenia and recurrent respiratory tract infections.

Case and methods: We present an 11-month-old girl with JBS. Her family history was unremarkable. Parental lymphocyte chromosomes were normal. Our patient has been examined with regard to dysmorphism and clinical abnormalities. Conventional chromosomal analysis as well as fluorescence in situ hybridisation (FISH) and whole genome sequencing (WGS) were performed.

Results: Our patient was delivered by Caesarean section and exhibited reduced birth measurements. Her dysmorphic features include a myopathic face, hypertelorism, low-set ears, anteverted nares, broad, sunken nasal root, brachydactyly, minimal syndactyly D2/ D3 at both sides. Furthermore, she is prone to infections, shows thrombocytopenia, dystrophy, muscular hypotonia, hearing impairment, ventricular and atrial septal defect, microcephaly, feeding problems, and delayed psychomotor development. Initially performed WGS revealed not only a deletion (11q24.1 to 11qter) but also a duplication and triplication in the region 11q23.3 flanked by inversions. A deletion on 11q encompassing the JBS region was confirmed by conventional karyotyping and FISH - 46,XX,del(11)(q24.1). The rearrangement was most likely caused by chromothripsis. Chromothripsis („chromosome shattering“) which is an `at-once event', usually comprises a large number of clustered deletions with random reconnection of the remaining fragments by non-homologous end joining.

Conclusion: Our typically affected patient is the second reported individual with JBS caused by chromoanagenesis (likely chromothripsis). The complex chromosomal rearrangement of our patient comprises two duplications, two inversions and one deletion on one chromosome 11q. We will present the clinical findings of our patient and the underlying complex chromosomal rearrangement and discuss chromothripsis in the context of rare diseases.

11.15 CYTOGENETICS IN THE ERA OF GENOMIC MEDICINE: A RETROSPECTIVE STUDY OF 700 PATIENTS

Jonathan Lévy, Xénia Latypova, Séverine Drunat, Nathalie Couque, Yoann Vial, Corinne Collet, Adeline Bonnard, Nicolas Derive, Pierre Blanc, Yline Capri, Louise Goujon, Lyse Ruaud, Laurence Perrin, Andrée Delahaye-Duriez, Cyril Mignot, Boris Chaumette, Anna Maruani, David Germanaud, Pauline Gaignard, Céline Dupont, SeqOIA Bioinformatics Group, Alain Verloes, Anne Claude Tabet

Keywords: genome sequencing, SeqOIA, optical genome mapping, constitutional cytogenetics, structural variant, genomic rearrangements, intellectual disability, malformation syndromes, autism spectrum disorders

Constitutional cytogenetics focuses on identifying numerical and structural chromosome anomalies involved in genetic pathologies. Historically dependent on manual, time-consuming techniques such as karyotyping and FISH, the field has advanced with the advent of chromosomal microarray analysis (CMA), enhancing diagnostic yield by 5 to 15%.

As part of the *Plan France Médecine Génomique 2025* (PFMG 2025), genome sequencing is emerging as the preferred method for identifying and characterizing genomic alterations at the nucleotide level. In this study, we analyzed cytogenetic anomalies in the first 700 patient cases using short-read genome sequencing in SeqOIA laboratory, addressing three clinical indications: 1) intellectual disability (ID), 2) malformation syndromes, and 3) autism spectrum disorder/neurodevelopmental disorders without ID.

Genome sequencing revealed a broader spectrum of genomic alterations than traditional methods, uncovering rearrangements below CMA detection thresholds and gene-level structural anomalies such as translocations, inversions, and ring chromosomes. It enabled a more detailed characterization of the genomic architecture of complex chromosomal rearrangements (CGRs), particularly through the detection of newly reported recurrent chromosomal patterns (dup-trip-inv dup, dup-normal-dup, etc.)

Our study also highlights the limitations of short-read sequencing, especially for CGRs. In some cases, we complemented the analysis with optical genome mapping (Bionano), highlighting the complementary nature of these technologies in characterizing complex structural anomalies.

11.30 A FAMILIAL CASE OF 1P36 DUPLICATION SYNDROME

A FAMILIAL CASE OF 1p36 DUPLICATION SYNDROME

Gianluca Contrò [1], Roberta Zuntini[1], Veronica Bizzarri[1], Antonio Percesepe[2], Livia Garavelli [1]

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Copy number variants (CNV) involving the terminal region of the short arm of chromosome 1, have been linked to neurodevelopmental disorders associated with dysmorphic features. While 1p36 deletion syndrome is a well-defined condition, reciprocal duplication or triplication are less frequently observed and thus less well known. We describe two novel patients (mother and daughter) carrying a chromosomal rearrangement resulting in a duplication of the short arm of a chromosome 1, within the 1p36.33p36.32, extended within position (GRCh37) 835601 and 4367216 and a size between of 3.5 and 4 Mb. FISH analyses revealed that the duplication is due to a derivative chromosome 16 with the interstitial duplication. The

daughter exhibited a complex clinical picture characterized by neurodevelopmental delay - mostly involving speech ability; she required school support. Facial dysmorphisms consist in wide forehead with bitemporal constriction, thin eyebrows, bilateral ptosis, wide nasal root with broad bulbous tip, low-set ears with hypoplastic lobe. A cutaneous dyschromic area in the left lumbar location with jagged margins has been observed. Spinal X-ray studies showed a lumbar and dorsal asymmetry with a scoliotic posture. Her mother, who carries the same chromosomal aberrations, shows some overlapping clinical features with a mild/moderate developmental delay and some common facial dysmorphisms, consisting in bilateral ptosis with hypertelorism, wide nasal root with a bulbous nasal tip and short neck.

The phenotypic spectrum observed in our patients stands in the middle between that reported in cases with 1p36 duplication (in association or not with other CNV or chromosomal anomalies) and cases with the triplication of the same region. Among the affected subjects known to date, the duplication seems to lead to a less severe condition. This last observation is reinforced by the fact that the majority of the subjects inherited the duplication from a parent. On the other hand, the triplication seems to lead to a more severe condition, with more pronounced neurodevelopmental issues and a higher incidence of dysmorphisms and epilepsy. Our report leads us to speculate that duplication and triplication share some common features and that the severity of the disorder is correlated to the number of extra copies.

11.40 16P13.3 DELETION UNIFYING OSTEOPETROSIS AND CONGENITAL DIARRHEA

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In this report we present a female infant displaying thrombocytopenia, increased bone density, and the observation of pale optic disc symptoms consistent with the diagnosis of osteopetrosis. However, the patient had non-infectious, blood- and mucus-free diarrhea, which osteopetrosis could not explain. Clinical exome sequencing and chromosomal microarray analysis identified a a rare 39 kb homozygous deletion (Fig. 1) on chromosome 16p13.3 encompassing the osteopetrosis-related CLCN7 gene and the recently annotated PERCC1 gene related to congenital diarrhea following the discovery by Oz-Levi et al. (2019) that non-coding regions can control the gastrointestinal expression of PERCC1. Pangrazio et al. reported similar deletion was observed, though it was associated with pseudomembranous colitis-related diarrhea,. Our case extends the phenotype associated with 16p13.3 deletions, as truncating variants in CLCN7 alone have not been known to present with diarrhea. The case confirms the critical region on chromosome 16 identified by Oz-Levi et al. as integral to congenital diarrhea. The finding advocates for the inclusion of 16p13.3 deletions in the differential diagnosis for patients with osteopetrosis and congenital diarrhea, reinforcing the significance of a genomic approach in atypical presentations and highlighting the potential for broader genetic implications in cases with congenital diarrhea.

Key words: Congenital diarrhea, Osteopetrosis, CLCN7, PERCC1, 16p13.3 deletion

Figure 1 : The 39 kb deletion on chromosome 16p13.3 including the C16orf91, CCDC154, and the exon 2–25 of the CLCN7 gene. The PERCC1 gene, which was recently annotated to the region between the C16orf91 and CCDC154 genes, was not included in the original image.

11.50 CLINICAL DIAGNOSIS VS MOLECULAR CONFIRMATION FOR A PATIENT WITH PARTICULAR PHENOTYPE AND INTELLECTUAL DELAY IN RING CHROMOSOME 15 SYNDROME

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Case presentation: Personal history: 12 year old boy, first child in the family with two children (sister healthy), premature (8 months), recurrent infections, recurrent vomiting in postnatal period and absent deglutition reflex in the neonatal period (gastrostomy until 5 years) Initial diagnostic: Cornellia de Lange Syndrome by phenotype and clinical criteria;
Consult reveal: Delay in neuropsychic development and language; Height -122.2 cm (below the 3rd percentile) with suggestive signs of skeletal dysplasia; Brachycephaly - confirmed by CT detects cerebral atrophy, disproportionate growth and dysmorphic facial features: triangular facies, microphthalmia, sinophrys, micrognathism, wide nasal base, thin lips, dysplastic ears, short neck, brachydactyly, clinodactyly V finger-right foot; Genitalia: cryptorchidism and hypoplasia of the penis. Multiple hypopigmented skin patches, one cafe au lait spot.
Assessment of growth hormone (GH) secretion based on stimulation tests reveal partial GH deficiency.
2012: Karyotype: 46,XY, r(15)(p11.2q26) Molecular results 2023: Del/Dup (CNV) analysis using the Comprehensive Skeletal Dysplasia identified a heterozygous deletion seq[GRCh37] del(15)(q26.3), chr15:g.100636501_101928130 encompassing exons 1-15 of *ADAMTS17*, and whole *CHSY1* gene. This deletion is estimated to cover the genomic region 15:100636501-101928130 and is at **least 1.3 Mb in size**. This variant is a gross deletion on chromosome 15, involving the terminal band q26.3. This deletion encompasses 10 protein coding genes, of which 6 are OMIM Morbid genes: *ADAMTS17, ALDH1A3, CERS3, CHSY1, LINS1,* and *LRRK1*, all of which are associated with disorders inherited in autosomal recessive manner.The genes located terminal of this deletion are not covered by the assay; this region contains 5 protein coding genes. Using this method, we cannot know exact breakpoints of the deletion, so the exact size and genomic position are unknown.

The patient is currently receiving somatotropin treatment, speech therapy and cognitive behavior therapy.

Discussion and conclusion: With a highly variable phenotype Ring Chromosomes 15 Syndrome cold have some overlapping clinical findings with Cornelia de Lange Syndrome so molecular diagnosis could differentiate the diagnostic. Do we need more accurate tests for a better clinical characterization? It would be sufficient to choose a panel with a limited number of genes or would be indicated WES, WGS in those cases? Could bring new information to predict the evolution and possible complications?