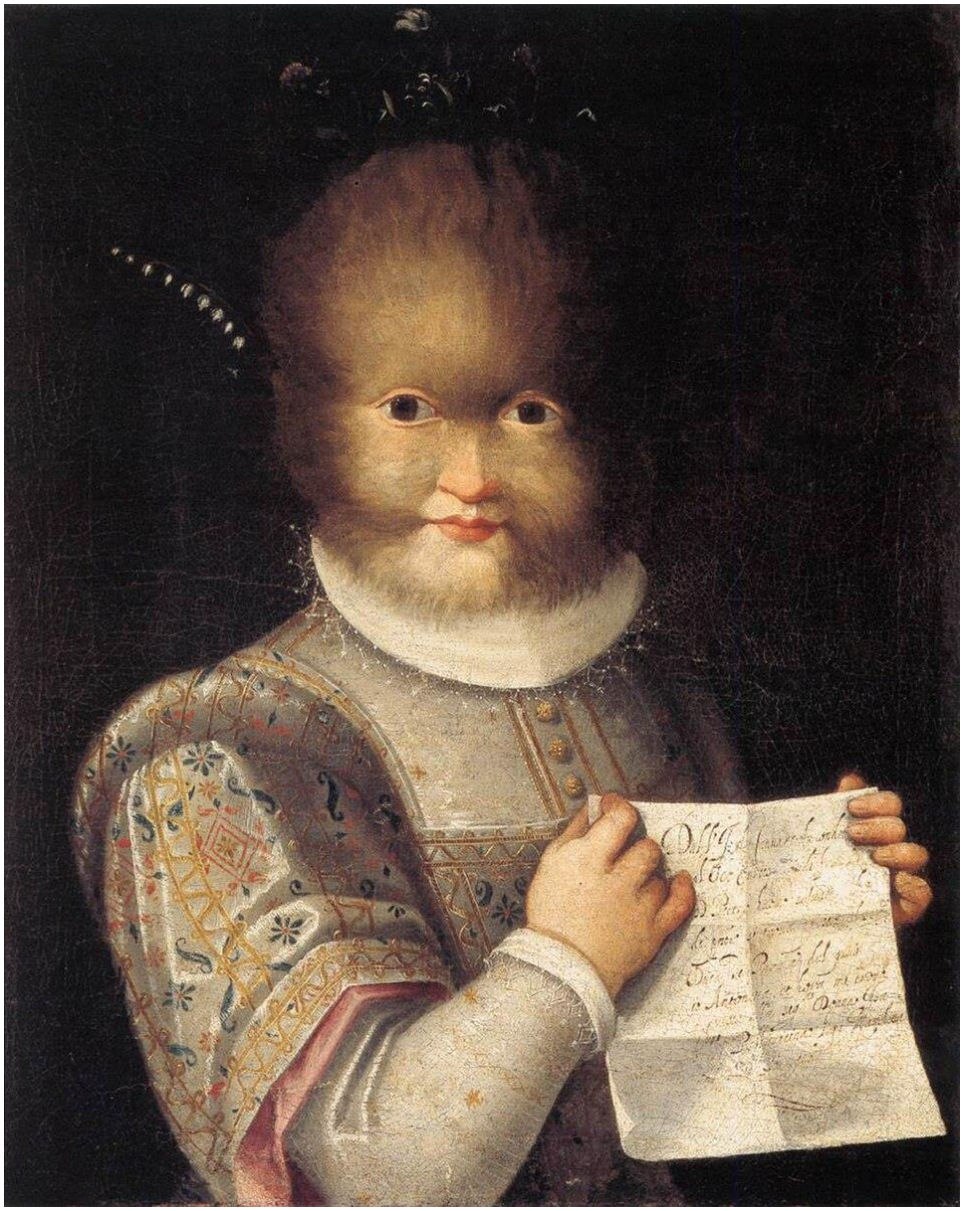
ABSTRACT BOOK

EURODYSMORPHO 2026

36th EUROPEAN MEETING ON DYSMORPHOLOGY

September 16-19 2026, Pavia University



Portrait of Antonietta GONSALVUS by Lavinia Fontana - 1595 (Blois castle, France)

ITHACA

Wednesday 16 September

Session 1 - Neurodevelopmental disorders

15:15, HETEROZYGOUS ALTERATIONS OF GTF2I AT THE WILLIAMS-BEUREN SYNDROME'S LOCUS CAUSE A NEURODEVELOPMENTAL DISORDER

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Purpose: Williams-Beuren syndrome (WBS) is a well-known neurodevelopmental disorder caused by a copy-number loss at the 7q11.23 locus. Although the 1.5-1.8 Mb recurrent deletion carries several genes of interest, no single gene has been identified in which pathogenic variants cause a neurodevelopmental phenotype. At this locus, *GTF2I*, encoding the general transcription factor II-I, has been considered as the main candidate gene for the cognitive and behavioural phenotype of WBS, based on clinical observations of cases with atypical 7q.11.23 deletions and functional studies in humans and mice.

Methods: Individuals with a neurodevelopmental disorder were identified through a multicentre collaboration using GeneMatcher and the ERN-ITHACA network. They remained undiagnosed following genome/exome sequencing. Clinical evaluations were performed in each participating centre.

Results: We identified seven unrelated individuals with de novo variants in *GTF2I* (two non-sense, two splice-site, one missense, one indel and one intragenic deletion). We also identified one individual with a WBS phenotype and low *GTF2I* expression identified by RNA

sequencing. All eight individuals presented with global developmental delay and facial dysmorphic features, with speech delay and/or autistic features in seven cases. The effect of the two splice-site variants was confirmed by RNA sequencing.

Conclusion: Pathogenic heterozygous *GTF2I* variants cause a neurodevelopmental disorder characterised by global developmental delay with facial dysmorphic features, partly resembling the phenotype observed in individuals affected with WBS.

Keywords: Genomics; RNA-Seq ; genome ; GTF2I ; Williams-Beuren syndrome ; neurodevelopmental disorder

15:30, AUTONOMIC DYSFUNCTION PROFILING OF MALAN SYNDROME USING PEDIATRIC AUTONOMIC SYMPTOM SCALES

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Background

The autonomic nervous system (ANS) is essential for body homeostasis, and its dysfunction, defined as dysautonomia, is increasingly recognized as a contributor to disease burden in neurodevelopmental/psychiatric disorders (NPDs), although it remains underdiagnosed. Malan syndrome (MALNS), an ultra-rare NPD caused by *NFIX* haploinsufficiency, has been associated with sporadic autonomic symptoms and autistic-like features, but their extent and clinical relevance have not been systematically investigated.

Results

We applied the Pediatric Autonomic Symptom Scales (PASS) to a large, molecularly confirmed and clinically homogeneous MALNS cohort (N=65), and compared results with previously characterized autism spectrum disorder (ASD), NPD, and healthy control populations. Our findings demonstrate a clear and clinically relevant burden of autonomic dysfunction in MALNS, while only partial overlap with ASD-specific profiles was evidenced. Symptom-level analysis distinguished features likely attributable to primary ANS dysfunction, such as cardiovascular symptoms, thermoregulatory issues, altered secretomotor activity,

hypoalgesia, and sensory processing anomalies, from those secondary to other MALNS-related traits. Notably, PASS results also suggest that the behavioral phenotype appears to be primarily driven by anxiety, language impairment, intellectual disability, and adaptive dysfunction rather than a core autistic profile.

Conclusions

Our study, which represents the first systematic assessment of ANS dysfunction in a rare genetic NPD, underscores the importance of integrating structured ANS assessment into routine evaluation and management of MALNS. More broadly, this work establishes a model for investigating dysautonomia in other rare disorders, with implications for improving diagnostic accuracy, patient stratification, and targeted care.

15:45, NUS1-RELATED DISEASE: UNCOVERING HIDDEN CLINICAL FEATURES AND NOVEL MUTATIONAL HOTSPOTS

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NUS1 encodes the transmembrane protein Nogo-B receptor, which is crucial for dolichyl phosphate biosynthesis, a lipid essential for posttranslational protein modification. Two distinct *NUS1*-associated genetic entities have been identified: the autosomal dominant neurodevelopmental disorder 55 with seizures (NDD55), caused by heterozygous,

predominantly truncating variants, and the autosomal recessive congenital disorder of glycosylation type IaA (CDG1AA), associated with biallelic missense pathogenic alterations. Here, we present the largest *NUS1* cohort reported to date, providing a comprehensive characterization of the clinical and molecular spectrum of 41 new and 61 previously described individuals with heterozygous *de novo* or inherited variants. The *NUS1*-associated phenotype is primarily characterized by neurodevelopmental delay (ND) with mild to moderate intellectual disability (ID), although few individuals present with normal cognition. Epilepsy and movement disorders, most notably myoclonus, tremor, and ataxia, also represent major clinical features. We highlight several previously overlooked clinical manifestations including behavioral abnormalities, psychiatric disorders, muscular hypotonia, and hearing loss. Next to the so far only description of two siblings with CDG1AA we included in our study three additional individuals with biallelic *NUS1* missense alterations. They exhibited a more severe phenotype with profound ND and ID, earlier-onset epilepsy, along with microcephaly and ocular anomalies, not reported in heterozygous individuals so far, supporting a clear genotype-phenotype correlation. Heterozygous *NUS1* variants included 50 truncating nonsense mediated decay (NMD)-inducing, 16 truncating NMD-escaping and 11 non-truncating alterations. The analysis of this large *NUS1* cohort enabled the identification of recurrent variants and two novel mutational hotspots: one within the functional undecaprenyl pyrophosphate synthase domain and another in a short segment spanning amino acids 86-103, which is located outside of previously known domains. Three-dimensional protein modelling suggested that this short segment likely plays a critical role in stabilizing the C-terminal catalytic region of Nogo-B receptor. In conclusion, this study substantially broadens the phenotypic and molecular landscape of *NUS1*-associated disease and establishes the basis for improved variant classification and diagnosis.

16:00, ASPM RELATED MCPH5 IN ADULTHOOD IN A CONSANGUINEOUS FAMILY: VARIABLE NEUROCOGNITIVE AND DYSMORPHOLOGICAL FINDINGS IN TWO SISTERS

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Background

Biallelic pathogenic variants in *ASPM* cause autosomal recessive primary microcephaly type 5 (MCPH5), a neurodevelopmental condition classically characterized by congenital or early onset microcephaly, craniofacial dysmorphic features, and variable intellectual disability. MCPH5 is the most common cause of autosomal recessive primary microcephaly, yet long-term neurocognitive outcomes in adulthood remain poorly characterised in the literature. Here we present two adult sisters with variable expressivity of neurologic findings.

Methods

Clinical exome sequencing was performed for proband using SOPHiA Clinical-Exome Solution v3. Chromosomal microarray analysis (Infinium Global Screening Array Cyto (GSA-Cyto); Illumina iScan platform) was performed for her sister.

Results

The proband, 25-year-old female with severe neurodevelopmental profile had severe microcephaly (SD Score: -15.48,), short stature (SD Score: -4.1), limited expressive speech, and a history of febrile and afebrile seizures. Craniofacial features included a sloping forehead, prominent ears, and micrognathia/retrognathia. Additional associated findings included macroglossia with persistent tongue protrusion and mirror movements of the hands. The homozygous truncating *ASPM* variant NM_018136.5:c.8892G>A;p.(Trp2964Ter) was identified and classified as pathogenic.

Her sister, 34-year-old female, shared severe microcephaly (SD Score: -8.99), short stature (SD Score: -2.57) and overlapping craniofacial features, supporting the MCPH5; however, her cognitive profile was milder. She could read and write and communicated with simple sentences, although notable memory impairment and adaptive difficulties were present. Karyotyping and microarray analysis were non diagnostic, targeted Sanger based segregation analysis for the familial *ASPM* variant is ongoing.

Conclusion

We report two adult sisters with severe microcephaly but the proband demonstrates a more severe neurodevelopmental profile with limited expressive speech and a seizure history, while her older sister retains functional communication, and greater independence despite prominent dysmnesia and adaptive difficulties. These findings shows that MCPH5 should be considered across a spectrum of cognitive severity, and that molecular confirmation remains essential for accurate diagnosis. Reporting adult outcomes in *ASPM*-related MCPH5 is clinically valuable, as it informs genetic counselling, realistic prognostic expectations for families, and the broader natural history of this condition beyond childhood.

16:10, A NOVEL MISSENSE VARIANT IN TUBB2B IN A CONSANGUINEOUS INFANT: PSEUDOGENE INTERFERENCE OBSCURING TRUE ZYGOSITY AND EXPANDING THE PHENOTYPIC SPECTRUM OF BIALLELIC TUBULINOPATHY

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Background: Heterozygous pathogenic variants in *TUBB2B* cause complex cortical dysplasia with other brain malformations type 7 (CDCBM7; MIM:610031), characterised by pachygyria, polymicrogyria, corpus callosum anomalies. More recently, biallelic *TUBB2B* variant has been described in a single family with a phenotypically distinct and potentially more severe neurological syndrome (PMID: 28013290). The full clinical spectrum of the recessive form remains incompletely defined. Here we report a 16-month-old male from a consanguineous family with brain malformations with a *TUBB2B* missense variant.

Methods: Clinical exome sequencing (CES) was performed (SOPHiA ClinicalExomeSolutionv3 kit, NextSeq2000). Sanger sequencing was performed for a missense variant for the confirmation of zygosity and parental segregation analysis. Chromosomal microarray was performed using Infinium GlobalScreeningArray-Cyto on Illumina-iScan with NxClinical software.

Results: The proband was born at 39+3 weeks to first-degree cousin parents, with no family history of neurological disease. Neonatal brain MRI demonstrated inferior vermis hypoplasia, partial corpus callosum dysgenesis, and mild colpocephaly. Progressive severe microcephaly was documented (-3.5 SDS at 3 months, -5.3 SDS at 13 months). Dysmorphic features included epicanthus, anteverted nares, mild retrognathia, narrow forehead with frontal hypertrichosis, deep and interrupted palmar creases, and a left ear helix fold anomaly. Neurologically, axial hypotonia with preserved deep tendon reflexes and no seizures was noted. Bilateral restricted lateral gaze was observed. At 16 months, he is not yet weight-bearing or walking. CES identified a novel missense variant in *TUBB2B* gene, NM_178012.5:c.658C>G (p.Pro220Ala), classified as a variant of uncertain significance and IGV analysis revealed a VAF of approximately 75%, raising the possibility of homozygosity. Given pseudogene complexity (*TUBB2BP1*), Sanger sequencing was performed; however, results were difficult to interpret definitively due to pseudogene interference. Both parents were heterozygous on Sanger sequencing, consistent with a potentially homozygous state in the proband. Importantly, microarray analysis revealed that the *TUBB2B* locus resides within a 3.6 Mb region of homozygosity, providing independent support for homozygosity of the identified variant.

Conclusion: This case illustrates two important challenges in tubulinopathy diagnostics: first, pseudogene-related technical artefacts can obscure true zygosity in *TUBB2B*, leading to potential misclassification of a homozygous variant as heterozygous; second, the neuroimaging and clinical profile (inferior vermis hypoplasia, corpus callosum dysgenesis, severe progressive microcephaly, axial hypotonia, restricted lateral gaze, and significant motor delay without spasticity), aligns more closely with the rare recessive *TUBB2B* phenotype than the classical dominant CDCBM7. This report can add to the limited literature on biallelic *TUBB2B* variants and shows the necessity of pseudogene-aware sequencing strategies, careful zygosity assessment, and the complementary role of SNP-based microarray

in detecting runs of homozygosity in consanguineous families with tubulinopathy-spectrum brain malformations.

16:20, A NOVEL HOMOZYGOUS INTRONIC POLRMT VARIANT IN TWO SIBLINGS WITH SEVERE NEURODEVELOPMENTAL DISORDER: EXPANDING THE MOLECULAR SPECTRUM OF COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY 55

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Background: Combined oxidative phosphorylation deficiency 55 (COXPD55) is an ultra-rare autosomal recessive mitochondrial disorder caused by biallelic variants in the *POLRMT* gene, which encodes the mitochondrial RNA polymerase.

Case presentation: We report two affected siblings, a brother and a sister, born to healthy non-consanguineous Caucasian parents with an unremarkable family history. Both patients presented with severe global developmental delay, absent speech, lack of sphincter control, profound intellectual disability, behavioral abnormalities, and growth parameters at the lower percentiles. Additional clinical features included congenital bilateral cataracts and early-onset hypotonia in the male sibling, while the female sibling presented with strabismus.

The diagnostic workup in the male initially included conventional karyotyping, methylation analysis of chromosome 15q, and whole-exome sequencing, all of which yielded negative results. Chromosomal microarray analysis performed in the female sibling was also negative. Subsequently, trio whole-genome sequencing was performed in both siblings and their parents. This analysis identified the homozygous intronic variant c.3581+5G>A in *POLRMT* in both affected individuals, while both parents were confirmed to be heterozygous carriers.

Discussion: Biallelic *POLRMT* variants have been associated with COXPD55, a disorder characterized by impaired mitochondrial transcription and defective oxidative phosphorylation. Emerging reports have expanded the phenotypic spectrum of this condition, which commonly includes developmental delay, hypotonia, short stature, intellectual disability, and severe language impairment. Ophthalmological manifestations, including progressive external ophthalmoplegia, have also been described. Considerable clinical variability has been reported among affected individuals.

The c.3581+5G>A variant identified in this family has not previously been reported and is currently classified as a variant of uncertain significance. To further investigate its pathogenicity, RNA sequencing studies are currently underway to assess its impact on splicing and transcript expression. Demonstration of impaired *POLRMT* transcription would provide additional evidence supporting the pathogenic role of this variant and the molecular diagnosis.

Conclusions: This report further expands the clinical spectrum associated with *POLRMT*-related disease and highlights the value of comprehensive genomic testing, including whole-genome sequencing, in individuals with profound intellectual disability and severe developmental delay, particularly when speech is markedly affected.

Session 2 – Neurodevelopmental disorders

17:00, Invited Talk: Huw Dorkins

17:45, CLINICAL CHARACTERISATION OF A COHORT HARBOURING MAP2K1 AND MAP2K2 VARIANTS: A 20-YEAR SINGLE CENTRE EXPERIENCE REFLECTING THE PHENOTYPIC CONTINUUM BETWEEN CARDIO-FACIO-CUTANEOUS AND NOONAN SYNDROME.

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Background

MAP2K1 and MAP2K2, respectively encoding MEK1 and MEK2 kinases, are established RASopathy genes predominantly associated with Cardio-Facio-Cutaneous (CFC) syndrome, although their full phenotypic spectrum remains incompletely defined.

Methods

In this retrospective study, we describe a cohort of 15 patients carrying pathogenic or likely pathogenic variants in MAP2K1 (n=14) or MAP2K2 (n=1), ascertained over a 20-year period at a single French national reference centre. Clinical and molecular data were collected through the ILIAD Registry using standardised Human Phenotype Ontology terminology.

Results

Among MAP2K1-positive individuals, the phenotype was clinically interpreted as CFC syndrome in nine patients, as Noonan syndrome in four patients, and as a milder unclassified form of RASopathy with predominant neuromuscular involvement. The CFC subgroup exhibited the greatest neurodevelopmental burden, with constant motor and speech delay, severe intellectual disability, frequent epilepsy requiring polytherapy, and prominent

ectodermal involvement. Patients classified as Noonan syndrome showed a milder and more variable cognitive profile. Cardiac involvement, predominantly pulmonary valve stenosis and hypertrophic cardiomyopathy, was present across subgroups. Identical MAP2K1 variants were identified in individuals with different clinical diagnoses.

The MAP2K2 patient exhibited a phenotype more suggestive of CFC

Conclusion

These findings underscore the limitations of phenotype-based classification and support the concept of a continuous RASopathy spectrum, highlighting the importance of longitudinal, genotype-informed follow-up. Further case descriptions, ideally from larger cohorts, are essential to fully delineate the clinical spectrum and natural history of MEK-related RASopathies.

17:55, SPECIAL POPULATION REQUIRE SPECIAL APPROACH: GENETICS FINDINGS AMONG THE SINTI POPULATION IN REGGIO EMILIA, ITALY

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Background: The Sinti population is a subgroup of the Romani ethnic group with its origins in north-western India. Despite being historically nomadic, they become settled throughout the years, establishing different nuclei in Central and Western Europe (Germany, France, and northern Italy). Among the different groups currently existing in Italy, a large one is specifically present in the Reggio Emilia area (Emilia-Romagna region, in the north of Italy). The cultural and physical isolation of this population has resulted in a high prevalence of endogamous marriage, with a high level of consanguinity As a consequence, the Sinti population exhibits several rare disorders, mostly recessive and due to private variants of the founder.

Material and Methods: We retrospectively collected the genetic and clinical information from 43 affected individuals belonging to the Sinti population resident in the Reggio Emilia area.

Results: Here we report a list of disorders with a known molecular confirmation (pathogenic or likely pathogenic variants, according to ACMG guidelines) detected in the Sinti population in Reggio Emilia, Italy (Table 1).

Conclusions: Our report contributes to expand the knowledge of rare conditions found among the Sinti population and their clinical presentation. The high mortality and morbidity of some of these conditions calls for a timely diagnosis in order to provide proper assistance. Prior knowledge of the pathogenic variants enriched in this group can expedite the diagnostic process and is essential for establishing the recurrence risks and the prenatal options during pregnancy. Finally, a specific-population approach appears to be needed in such clinical set.

TABLE 1. ***Inherited disorders with a molecular confirmation in Sinti population.***

GENE	***GENETIC VARIANT IDENTIFIED***	***CLINICAL CONDITION (#OMIM)***
SMOC1 NM_001034852.3	c.648insA, p.(Asn217Lysfs*12)	Microphthalmia With Limb Anomalies (**#** 206920)
UFM1 NM_016617.4	c.-155_-153del	Leukodystrophy, Hypomyelinating, 14 (# 617899)
DMD NM_004006.3	c.(1992+1_1993-1)_(2168+1_2169-1)dup	Muscular Dystrophy, Duchenne type (# 310200)
SGCG NM_000231.3	c. 848G>A, p.(Cys283Tyr)	Muscular Dystrophy, Limb-Girdle, Autosomal Recessive 5 (# 253700)
CYP21A2 NM_000500.9	c.293-13A/C>G, p.(Leu143Pro)	Adrenal Hyperplasia, Congenital, Due To 21-Hydroxylase Deficiency (# 201910)
GH1 NM_000515.5	45 kb intragenic deletion	Isolated Growth Hormone Deficiency, Type Ia (# 262400)
F8 NM_000132.4	c.6172G>A, p.(Ala2039Pro)	Hemophilia A (# 306700)
CTDP1 NM_004715.5	c.506+389C>T. p.(?)	Congenital Cataracts, Facial Dysmorphism, And Neuropathy (# 604168)
CHD7 NM_017780.4	c.6996G>A, p.(Trp2332*)	CHARGE Syndrome (# 214800)
TNNT3 NM_006757.4	c.187C>T, p.(Ala63CYs), heterozygous	Arthrogryposis, Distal, Type 2B2 (# 618435)
ACADS NM_000017.4	c.310_312del p.(Glu104del)	Acyl-CoA Dehydrogenase, Short-Chain, Deficiency Of; ACADSD (# 201470)

RYR1 NM_000540.3	c.7048G>A, p.(Ala2350Thr)	Congenital Myopathy 1a, Autosomal Dominant, With Susceptibility To Malignant Hyperthermia (# 117000)
Chr11	Mosaic paternal UPD of 11p15.5-p15.4	Beckwith-Wiedemann syndrome (#130650)
DMPK NM_004409.5	CTG repeat expansion	Myotonic dystrophy 1 (# 160900)
TSPEAR NM_144991.3	c.1870G>T p.(Glu624*)	Ectodermal Dysplasia 14, Hypohidrotic/Hair/Tooth/Nail Type (# 618180)

18:05, PHENOTYPIC MIMICRY AND DUAL DIAGNOSES IN PATIENTS EVALUATED FOR BECKWITH-WIEDEMANN SPECTRUM

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Background: Beckwith-Wiedemann spectrum (BWSp) is a clinically and molecularly heterogeneous imprinting disorder characterized by overgrowth and tumor predisposition. Because of its broad phenotypic spectrum, overlap with other genetic conditions may create diagnostic challenges and increase the risk of attribution bias when discordant findings are interpreted within a BWSp framework.

Aim: To assess the clinical relevance of atypical findings through deep phenotyping in patients investigated for suspected BWSp, with the aim of identifying overlapping phenotypes, dual diagnoses, and underrecognized clinical associations.

Materials and Methods: We retrospectively reviewed 279 patients evaluated for suspected BWSp between 2007 and 2026. All patients with a BWSp clinical score ≥2 undergoing molecular investigation were included. Ninety-two patients (33%) had molecularly confirmed BWSp, of whom 71/92 (77.2%) fulfilled the clinical diagnostic criteria (clinical score ≥4). Among molecularly negative patients, 51/187 (27.3%) also met clinical diagnostic criteria. Deep phenotypic reassessment focused on identifying clinical features not readily fitting a conventional BWSp phenotype and correlating these findings with subsequent genetic investigations.

Results: Among the 143 patients with either molecularly confirmed BWSp or a clinical diagnosis of BWSp (clinical score ≥4), atypical findings included neurodevelopmental manifestations (n=36, 25.2%), hematologic abnormalities (n=7/143, 4.9%), macrocephaly (n=4/143, 2.8%), major congenital cardiac anomalies (n=2), hearing loss (n=2), major dysmorphic features (n=2), retinitis pigmentosa (n=1), and peripheral neuropathy (n=1). Among molecularly negative patients fulfilling clinical BWSp criteria, additional investigations identified alternative diagnoses including *PIK3CA*-related overgrowth spectrum, Noonan syndrome, *DPF2*-related syndrome, and *WAC*-related disorder. One patient showed a likely dual diagnosis consisting of retinitis pigmentosa associated with a BWSp phenotype. Among molecularly confirmed BWSp patients, four dual diagnoses were identified: Charcot-Marie-Tooth disease, *PTEN* hamartoma tumor syndrome, *KMT2E*-related neurodevelopmental disorder, and Wolf-Hirschhorn syndrome.

Conclusions: Systematic assessment of atypical findings in patients with confirmed or suspected BWSp may uncover phenotypic mimics, dual diagnoses, and potentially expand the clinical spectrum of the disorder. Indeed, some discordant findings remained unexplained despite extensive investigation, raising the possibility of underrecognized BWSp manifestations that warrant further evaluation in larger, deeply phenotyped cohorts. Overall, our findings highlight the importance of deep phenotyping and maintaining diagnostic flexibility when discordant features are not fully explained within the conventional BWSp framework.

References: Brioude et al., Nat Rev Endocrinol. 2018 PMID: 29377879.

Thusrday 17 September

Session 3 - Dysmorphology

9:00, Invited talk:

9:45, THE BURDEN OF MISDIAGNOSIS: ONE EXAMPLE FROM THE DROP BY DROP PROJECT LEADS TO EXPAND THE SPECTRUM OF SPLICEOSOMOPATHIES

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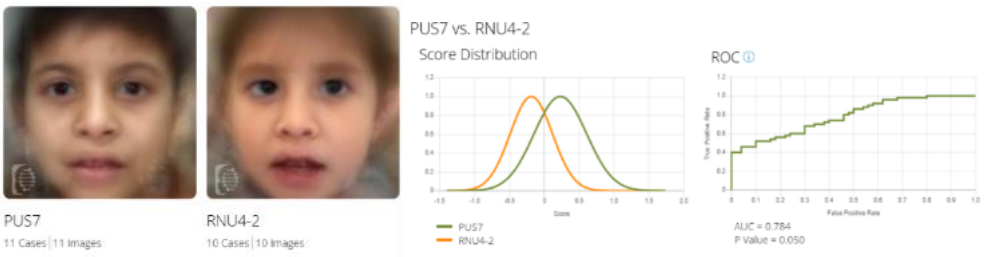
Defining a genetic diagnosis represents a challenging and stepwise process, often limited by the identification of alterations with unknown significance and constrained by current knowledge perspectives. Alterations in non-coding RNAs and in their modulating mechanisms are now emerging as one main possible explanation underpinning a large number of cases of neurodevelopmental disorders that have remained unsolved for many years. Among post transcriptional RNA modification, pseudouridylation is mediated by pseudouridine synthase (PUS) enzymes and its aberrations have been recently related to several human disorders. The latest description regards the *PUS7* gene (MIM# 616261), causatively associated to an extremely rare recessive disease characterized by postnatal microcephaly, neurodevelopmental impairment and minor dysmorphisms. Here we report a novel case of this poorly known disorder, diagnosed in a young girl referred to our Center after a misdiagnosis of Kleefstra Syndrome type 2. Her clinical picture was quite aspecific, featured by neurocognitive impairment, hypoacusia and peculiar facial traits. The former misdiagnosis was dismissed after the detection through whole genome sequencing of two composite heterozygous deletions in the *PUS7* gene. Guided by our gestaltic evaluation, we investigated through deep learning technology the possible clinical convergence among this condition and one main spliceosomopathy (SPs), ReNU syndrome (see Figures below: on the left the composite profiles of the two conditions. On the right the result of deep learning comparison).



Data from this exploratory analysis, together with recent evidence in literature, support the affinity between these conditions, suggesting that disorders of pseudouridylation might possibly be included among SPs. Aside from expanding the current knowledge about *PUS7* related disorder and to explore its nosological classification, one of the main aims of our report is to raise awareness of the impact of genetic labelling and misdiagnoses.

10:00, BEYOND THE "ONE GENE-ONE DISEASE" MODEL: A COMPARATIVE PERFORMANCE ANALYSIS OF AI PHENOTYPING TOOLS IN CHROMATINOPATHIES

Giulia Bruna MARCHETTI[1], Federica ALBERTI[1], Elvira VERDUCI[1,2], Francesca CAPPUCCINI[3,4], Valentina MASSA[2,5], Cristina GERVASINI[2,5], Maria IASCONE[3], Laura PEZZOLI[3], Donatella MILANI[1]

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Background: The clinical diagnosis of genetic syndromes strongly relies on the recognition of specific facial patterns. Recently, Artificial Intelligence (AI) has revolutionized the dysmorphological evaluation with tools like Face2Gene (F2G) and GestaltMatcher (GM). Chromatinopathies (CPs) are a growing group of rare disorders characterized by clinical and facial overlaps that pose a challenge for clinicians and AI-driven phenotyping.
Aims: This work aims to evaluate and compare the diagnostic accuracy of two different AI tools (F2G and GM) in the CPs's setting in order to investigate their reliability and trustability, weighting the burden of ultrarare diseases and ageing. Furthermore, we will ascertain gestaltic overlap among these conditions and perform exploratory analysis on functional classes of epigenetic genes.

Material and Methods: We performed a retrospective head-to-head comparison of F2G and GM performance on a cohort of 239 photographs from 181 molecularly diagnosed patients with 33 different CPs. We also divided photos into rare and ultrarare disorders according to the disease prevalence. We evaluated the diagnostic accuracy and the impact of age on AI's recognition ability. Additionally, using F2G research tool we performed multiclass comparisons on the main diagnosed groups in our cohort and on functional categories of epigenes.

Results: F2G and GM showed comparable diagnostic performance with a Top-3 sensitivity of 65% and 61% respectively. The diagnostic rates of both tools decline with age while the disease prevalence significantly influences F2G diagnostic accuracy. Multiclass analyses mainly highlighted the strong overlap between Wiedemann-Steiner and Rubinstein-Taybi syndromes. The same analysis performed on functionally distinct classes globally confirms phenotypical overlap within the epigenetic machinery.

Conclusion: AI tools are highly effective in recognizing well-characterized CPs but their sensitivity is significantly limited by patient age and disease rarity. Our results provide digital evidence of the biological overlap within CPs. As genetic nosology shifts toward "collective" nomenclature for syndromic families, AI tools must evolve to identify shared functional signatures, supporting clinicians in the diagnosis among increasingly complex genetic networks.

Keywords: Artificial Intelligence, Dysmorphology, Chromatinopathies

Additional information: This work was funded by "Fondazione Regionale per la Ricerca Biomedica" grant number 3441133.

10:15, MODIFIED FACIAL PHENOTYPE IN SYNDROMIC CHILDREN: A SOURCE OF DIAGNOSTIC UNCERTAINTY

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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	-	-

Session 4 - Unknowns

11:00, UNKNOWN CASE REPORT: A MALE PATIENT WITH PROGEROID PHENOTYPE

Paolo Fontana

Medical Genetics Unit - AORN San Pio - Benevento (Italy)

Male 4-year-old patient. He was born after 36 weeks of a pregnancy complicated by oligohydramnios and intrauterine growth restriction, with a birth weight of 1.760 Kg.

At birth he presented with a progeroid appearance, with microcephaly and marked prevalence of the neurocranium over the splanchnocranium, prominent venous network in the frontal region, long and prominent nasal bridge, low-set ears, thin lips. He also had mild

pyelectasis, unilateral cryptorchidism, atrial septal defect and bovine aortic arch. At the age of 4 he still exhibits a progeroid facial appearance, his weight and head circumference are at the 3rd percentile, and he presents with more than 10 café-au-lait spots. Karyotype, SNP-Array, WES and WGS didn't detect pathogenic variants.

11:10, ONE MORE UNDIAGNOSED A "MUST-BE GENETIC" CASE

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Date of Birth: May 5, 2017 **Clinical Presentation:** A 5-year-old girl (at time of first visit) presenting with a complex phenotype highly suggestive of a **RASopathy** or **Noonan syndrome**. Key clinical features include short stature, neurodevelopmental delay, a patent foramen ovale, few café-au-lait spots, and distinct facial dysmorphism (highly arched eyebrows, epicanthus, low-set ears, long philtrum, and upslanted palpebral fissures).

Genomic Testing Timeline

2019: Clinical Exome Sequencing (CES) – Bulgaria Initial testing identified a heterozygous variant in the **NF1** gene: **c.3884C>T, p.Thr1295Ile**. At the time, this variant was classified as **Likely Pathogenic**. However, segregation analysis revealed the variant was inherited from the patient's **asymptomatic mother**, complicating its clinical interpretation.

2022: Expanded Panel Testing – Invitae (USA) Seeking clarification, expanded testing was performed including RASopathies, Noonan Spectrum Disorders, and Skeletal Disorders panels. Reported **NF1 c.3884C>T:** Reclassified as a **Variant of Uncertain Significance (VUS)** and multiple other VUSs in other genes not clearly associated with the phenotype.

2024: Re-evaluation and Whole Exome Sequencing (WES GRCh37) A 2024 re-evaluation and resequencing noted an additional VUS in **EPB41L1: c.2280C>G**, which is associated with neurodevelopmental disorders and dysmorphism.

2025: Most recently, **WES (**GRCh38**)** was conducted (Novogene) to further explore the genetic landscape with no pathogenic or likely pathogenic variant identified to explain the phenotype.

Conclusion and Clinical Impression

Despite being extensively tested, the patient remains without a definitive molecular diagnosis. The clinical suspicion continues to gravitate toward a **RASopathy/Noonan-like phenotype**, potentially driven by a complex "multi-hit" genetic architecture or yet unclassified variants. The NF1 and MAP3K7 variants remain the primary candidates of interest, though their inheritance is from an asymptomatic parent.

11:20, AN UNRESOLVED, LETHAL NEURODEVELOPMENTAL SYNDROME CHARACTERIZED BY MICROCEPHALY, MICROTIA, PIERRE-ROBIN SEQUENCE, AND SEVERE GROWTH RESTRICTION

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Introduction

We report on a female patient presenting with a severe, unrecognized, and ultimately lethal neurodevelopmental syndrome characterized by profound growth restriction, distinct craniofacial dysmorphism, and multi-system involvement, born to consanguineous parents.

Case Presentation

The patient, an only child to first-cousin parents, was born full-term via emergent C-section. She exhibited severe postnatal growth failure, microcephaly, global developmental delay, hypotonia, and infantile-onset seizures. Key features included a severe Pierre-Robin sequence requiring supplemental oxygen, developmental dysplasia of the hip, clitomegaly, recurrent infections, and central pyrexia.

Physical examination at 17 months of age revealed extreme growth failure and microcephaly: weight was 3 kg (-7.89 SD), height was 58 cm (-6.73 SD), and head circumference was 41 cm (-4.09 SD). Striking dysmorphic features included a wide metopic region, bitemporal prominence, prominent eyes with downslanting palpebral fissures, midface retrusion, microtia with low-set, posteriorly rotated ears, and digital clinodactyly.

Brain MRI showed diffuse bifronto-parietal volume loss and a thinned corpus callosum. Abdominal ultrasound revealed bilateral increased renal cortical echogenicity. Chromosome analysis was normal (46,XX). Exome sequencing was negative for a primary phenotypic cause, revealing only a secondary pathogenic heterozygous variant in *BRCA2* (HBOC predisposition)

and non-contributory heterozygous carrier states for *DYNC2H1* and *FECH*. The patient passed away shortly after this evaluation at 17 months of age

Conclusion

This constellation of features may represent a novel autosomal recessive neurodevelopmental disorder. We present this unresolved case to seek diagnostic insights and potential phenotypic matches from the dysmorphology community.

11:30, AN UNRESOLVED SYNDROMIC CONDITION COMBINING CRANIOFACIAL DYSMORPHISM, BRANCHIAL ANOMALIES, NEURODEVELOPMENTAL DELAY AND NEONATAL SKIN FRAGILITY

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Background:
The recognition of rare syndromic entities remains challenging in children presenting with overlapping developmental, dysmorphic and congenital anomalies, particularly when first-tier genetic investigations are unrevealing.

Case report:
We describe a 3-year-old girl referred for genetic evaluation due to developmental delay, growth failure and multiple congenital anomalies. Family history was unremarkable, except for maternal aortic valvular disease requiring mechanical valve replacement. The patient has one healthy sibling. Pregnancy was notable for in utero exposure to warfarin during the first month of pregnancy and prenatal suspicion of fetal malformations that were not confirmed postnatally.
She was born at 35+6 weeks of gestation. The neonatal period was notable for respiratory distress, a single seizure episode and striking cutaneous abnormalities characterized by skin detachment and hyperkeratotic lesions, raising suspicion of epidermolysis bullosa. Persistent postnatal growth impairment was observed, with weight, length and head circumference below the 3rd percentile, despite progressive catch-up growth.
Clinical examination revealed a distinctive craniofacial gestalt including large ears, epicanthal folds, broad nasal bridge, hypoplastic alae nasi, short columella and microretrognathia. Additional findings included bilateral suspected branchial anomalies with cervical

fibrochondromatous lesions, more prominent on the left side, as well as marked sialorrhea. She remains under multidisciplinary follow-up for psychomotor developmental delay.
Exome sequencing performed in the proband did not identify pathogenic or likely pathogenic variants relevant to the phenotype.

Conclusion:
This patient presents a striking yet currently unclassifiable syndromic phenotype combining craniofacial dysmorphism, branchial abnormalities, neurodevelopmental impairment and neonatal skin fragility. Although prenatal warfarin exposure may have contributed to some clinical features, the overall phenotype appears broader and remains insufficiently explained by a teratogenic etiology alone. The absence of a molecular diagnosis currently limits accurate genetic counselling, prognostic definition and tailored surveillance for the patient and her family. Clinical photographs will be presented at the meeting, and we welcome discussion and expert input regarding possible syndromic diagnoses or phenotype recognition.

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11:40, UNDIAGNOSED: PATIENT WITH LARYNGOMALACIA, MULTIPLE MALFORMATIONS AND DYSMORPHIC FEATURES WITHOUT A GENETIC DIAGNOSIS

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We report the case of a 2-year-old girl followed at our Genetics and Complex Disorders Unit for a syndromic condition characterized by dysmorphic features, severe tracheolaryngomalacia, neurodevelopmental impairment, and cardiac congenital anomalies, currently lacking a definitive genetic diagnosis.

The patient is the first child of non-consanguineous Albanian parents, with an unremarkable family history for congenital malformations, dysmorphisms and neurodevelopmental disorders. Conception occurred naturally and the mother denies personal history of recurrent pregnancy loss. Pregnancy was complicated by gestational diabetes treated with insulin. Prenatal investigations were normal. She was born at 39+1 weeks of gestational age by spontaneous delivery, with Apgar score of 9/9 and normal auxological parameters (birth weight 3405 g, length 49 cm, head circumference 33 cm). No perinatal and early post-natal complications were reported and the patient was discharged after 3 days from birth.

From the first weeks of life, the patient presented severe laryngotracheomalacia with persistent stridor, still persisting to date despite adequate somatic growth. Multiple

laryngotracheoscopies and radiological investigations were conducted, including CT scan of the neck and thorax, demonstrating narrowing of the trachea and of the left main bronchus. Currently the patient uses at home respiratory support with PEP mask and high-flow nasal cannula as needed.

At one month of age, neurological evaluation revealed microcephaly (with head circumference <10th percentile), generalized hypotonia, poorly organized motor repertoire, and impaired visual engagement. Brain MRI performed at two months showed reduced biometric parameters of the corpus callosum and posterior fossa in the context of microcephaly, with mild hemosiderin deposits in the lateral ventricles, predominantly on the left, consistent with sequelae of grade I germinal matrix-intraventricular hemorrhage. No additional structural or signal abnormalities of the brain parenchyma were identified. During subsequent follow-ups partial neurological improvement was observed; however, global developmental delay and axial hypotonia persist.

Cardiac evaluation for a systolic murmur identified an ostium secundum atrial septal defect, currently hemodynamically stable.

Physical examination reveals distinctive dysmorphic features, including square-shaped face, hypertelorism, downslanting palpebral fissures, cup-shaped ears, depressed nasal root, broad nasal bridge, and thin upper vermilion border. Additional clinical features include generalized joint laxity and severe sialorrhea.

Different genetic investigations were conducted. Array-CGH (400K) yielded normal results. Whole-exome sequencing (EXOME 30 TRIO) did not identify pathogenic or likely pathogenic variants clearly associated with the phenotype. Heterozygous variants of uncertain significance (VUS) were identified in the genes *CDKL5*, *SMARCC2*, and *JARID2* but their association to the described clinical picture lacks strong evidence. Subsequently, following the clinical suspicion of ReNU syndrome, targeted analysis of *RNU4-2* was performed, again with negative results.

The reported case highlights the diagnostic challenges posed by complex syndromic phenotypes with inconclusive investigations. In addition to further targeted genomic analyses and periodic re-evaluation of available sequencing data, may generate novel diagnostic hypotheses and contribute to a more comprehensive interpretation of the patient's phenotype, ultimately helping to clarify the underlying disorder.

11:50, PATIENT WITH MULTIPLE CONGENITAL MALFORMATIONS AND DYSMORPHIC FEATURES WITHOUT A GENETIC DIAGNOSIS

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The patient is a 13-year-old boy followed for multiple congenital anomalies, including anorectal malformations, choanal stenosis, patent ductus arteriosus, secundum atrial septal defect, tethered cord and Chiari malformation.

He is the only child of non-consanguineous parents. Family history is notable for cases of trisomy 21 on the maternal side. There is no history of miscarriages in the mother. He was born by urgent cesarean section due to non-reassuring cardiotocography. Birth weight was 2640 g, length 48 cm, and Apgar score was 9/9.

At birth, he presented with anorectal malformation, severe choanal stenosis, patent ductus arteriosus, a small atrial septal defect (3–4 mm) with left-to-right shunt, pulmonary hypertension, and tricuspid insufficiency. At one month of age, he underwent colostomy and dilation of the right nasal cavity.

Brain and spinal MRI showed Chiari type I malformation, with caudal herniation of the cerebellar tonsils through the foramen magnum and mildly reduced cerebrospinal fluid spaces at the cranio-cervical junction. At approximately 2 years of age, he underwent surgical untethering of the spinal cord.

His medical history is notable for recurrent obstructive bronchitis and frequent upper respiratory tract infections, as well as multiple allergies and mild developmental delay.

On physical examination, he presents with an asthenic habitus, asymmetry with the left scapula and shoulder higher than the right. Oral examination reveals severe malocclusion, a single central incisor and crowding of the lower dental arch. Bilateral preauricular fistulae are present. The chest is mildly excavated and asymmetric (right < left). Limb anomalies include clinodactyly of the fifth fingers, triphalangeal thumbs and posteriorly positioned halluces.

Array-CGH analysis identified a small duplication at 22q12.3 of uncertain significance. Molecular analysis of CHD7, SALL4, and SHH genes was negative for mutations and copy number variations. Whole exome sequencing (30 Mb) in trio was performed, identifying a heterozygous variant c.2690G>A (p.Arg897Gln) in the URB1 gene, inherited from the mother. Homozygous or compound heterozygous mutations in URB1 are known to cause Johanson-Blizzard syndrome, characterized by typical dysmorphic features including nasal wing aplasia

or hypoplasia, sensorineural hearing loss, imperforate anus, exocrine pancreatic insufficiency, tethered cord and congenital heart defects. However, according to ACMG guidelines, the identified URB1 variant is currently classified as a variant of uncertain significance (PM2). To date, a definitive diagnosis has not been established. Long-read sequencing analysis is currently ongoing.

Session 5 – Limb defects

12:05, AN UNDIAGNOSED SYNDROMIC PHENOTYPE COMBINING CRANIOFACIAL DYSMORPHISM, CRANIO-CERVICAL MALFORMATIONS AND BILATERAL PREAXIAL POLYDACTYLY

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Introduction: We describe a 2-year-8-month-old boy with a complex syndromic phenotype involving craniofacial, skeletal and central nervous system anomalies. Pregnancy history was unavailable due to absent prenatal follow-up.

Clinical case: The patient is the second child of non-consanguineous parents from Bangladesh. Craniofacial features include brachycephaly, wide fontanelles with sutural diastasis, mandibular hypoplasia with severe microretrognathia, hypertelorism, downslanting palpebral fissures, and low-set, posteriorly rotated crumpled ears. Limb anomalies include bilateral preaxial polydactyly with thumb duplication. Hypospadias is also present. The patient presents with global developmental delay.

Brain MRI demonstrates enlargement of the corpus callosum, pontine hypoplasia, cortical dysgyria, and cervical segmentation anomalies within the Klippel–Feil spectrum. Cranial and cervical CT confirms sutural diastasis and cervical butterfly vertebrae.
During his first year of life, the patient developed growth failure and recurrent postprandial vomiting requiring gastrostomy placement after exclusion of intestinal malrotation. Progressive occipito-cervical instability led to indication for occipito-cervical arthrodesis.

Metabolic investigations, echocardiography, and abdominal ultrasound are within normal limits.

Conventional karyotype, chromosomal microarray analysis, and extensive next-generation sequencing, including targeted panels for syndromic craniofacial disorders and multisystem ciliopathies as well as exome sequencing, are all negative.

Conclusions: Despite extensive clinical and genetic investigations, no unifying diagnosis has been established. The combination of craniofacial dysmorphism, cranio-cervical skeletal anomalies, central nervous system abnormalities, and preaxial limb malformations does not match a recognized syndromic condition. This case highlights the diagnostic challenges posed by complex multisystem phenotypes and may contribute to the future delineation of a previously unrecognized disorder.

12:15, BHLHA9-RELATED SPLIT HAND AND FOOT MALFORMATION

Authors: Nicola Walsh[1], Claudine Vavasseur[2], Marlese Dempsey[3], Sally Ann Lynch[14]

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Introduction

17p13.3 duplications are the most common aetiology of split-hand/foot malformation with long bone deficiency (SHFMLD) (Klopocki PMID: 22147889 2012). Penetrance of this genotype is difficult to predict making estimates regarding recurrence risk challenging. Duplication of the BHLHA9 gene is responsible for the ectrodactyly phenotype.

Our patient

We report a male infant who was 1 year and 1 month old at review. He was born to a healthy, unrelated couple after a normal pregnancy. There was no family history of note. At birth, he was noted to have symmetrical ectrodactyly of both hands. His feet were normal. He was otherwise healthy. X-ray of both hands showed five metacarpals bilaterally. Both hands have three sets of phalanges associated with the second, fourth and fifth fingers indicating a

deficient third ray of both hands. There were no other abnormalities. Postnatal investigations including abdominal ultrasound, cranial ultrasound, chest x-ray were normal.

On review in the genetics clinic, he was meeting his developmental milestones and exhibited normal social development. There were no concerns for a syndromic association with ectrodactyly. In particular, the patient did not exhibit any other skeletal malformations. Neither parent had evidence of any hand or foot malformations and there was no family history of limb malformations on either side.

- **Genotype**

Array CGH analysis for the proband showed a 203kb 17p13.3 duplication which encompasses BHLHA9: (1158399-1361008[hg20 GRCh38])x3. This duplication was unexpectedly maternally inherited. Family segregation identified the 17p13.3 in the index's maternal grandmother. The 17p13.3 duplication completely encompasses the BHLHA9 gene. Petit postulated BHLHA9 to be the dosage dependent gene causing ectrodactyly in this region (PMID: 23790188). No directly corresponding duplications to our patient's duplication are observed in gnomAD CNVs v4.1.0 however smaller duplications within the region involving BHLHA9 occur in this dataset which would be consistent with the non-penetrance of skeletal manifestations associated with this duplication.

Discussion

Our family shows non-penetrance of a 17p13.3 duplication associated with SHFMLD. Inheritance of the duplication has been reported in a minority of families in the medical literature. Furthermore, our case shows inheritance of a non-penetrant 17p13.3 duplication across multiple generations. The breakpoints of the duplication for our patient is distinct from the breakpoints reported for patients with 17p13.3 duplications in the literature to date (Fusco PMID: 28496997, Klopocki PMID: 22147889, Petit PMID: 23790188) which is in keeping with the non-recurrence of the duplicated region that has already been reported.

Klopocki PMID: 22147889 observed a sex bias resulting in more affected males than females, with higher risk of unaffected carriers having an affected male offspring compared to an affected female offspring (36% vs. 15%), but more severe phenotypic expression in females when affected. This is important for the family in light of reproductive genetic testing options available and aided their decision making.

12:25, MOSAIC CARDIOFACIOCUTANEOUS SYNDROME DUE TO A MAP2K1 VARIANT: A MULTIDISCIPLINARY CASE REPORT WITH FUNCTIONAL EVIDENCE

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We report the case of a 22-months-old male infant discussed within a structured genomic multidisciplinary team meeting. The patient is the second-born child of non-consanguineous parents; the family history is unremarkable. The pregnancy was complicated by gestational diabetes, hypothyroidism, and maternal CMV infection. Amniocentesis (46,XY; CMV-DNA negative), NIPT, and serial ultrasound examinations were all normal. He was born at 38+3 gestational weeks via caesarean section with normal birth parameters but presented with respiratory distress (APGAR 4/6/7), diffuse papular cutaneous lesions and required admission to the neonatal ICU. Abdominal ultrasound, ECG, echocardiography, and cranial ultrasound were all normal. At 3 months of age, he was readmitted following the onset of seizures in the context of global hypotonia and growth delay; the cutaneous lesions persisted. Investigations revealed a pathological EEG managed with pharmacological treatment and severe dysphagia requiring nasogastric tube placement; brain MRI was normal at this stage. Clinical examination revealed sparse hair, low-set ears, right-sided ptosis, strabismus, nystagmus, a low and depressed nasal bridge, macrostomia, and micrognathia. Genetic testing via an NGS RASopathies panel on skin biopsy identified a mosaic pathogenic variant c.157T>C, p.Phe53Leu in *MAP2K1* (VAF 24%), confirmed on blood (VAF 24%) and saliva (VAF 5.7%). *MAP2K1* encodes a component of the MAPK signalling pathway and is associated with autosomal dominant Cardiofaciocutaneous (CFC) syndrome. The variant is absent from population databases; however, the same amino acid substitution has been reported in a single previously published patient with mosaic CFC syndrome diagnosis. Functional studies in *Drosophila* and zebrafish demonstrated that the substitution is non-viable in the germline state. Following multidisciplinary evaluation, a diagnosis of mosaic CFC syndrome was established, consistent with the clinical phenotype and molecular findings. During follow-up, a PEG tube was placed, and antiepileptic therapy was initiated. Repeat brain MRI demonstrated mild hypoplasia of the corpus callosum and anterior commissure, and absence of the normal neurohypophysis T1 hyperintensity. Skin biopsy histopathology revealed a juvenile xanthogranuloma-like pattern. A solid tongue lesion was detected at 19 months of age and is currently awaiting histopathological assessment. This case contributes to the growing evidence for mosaic RASopathies caused by *MAP2K1* variants presenting as CFC syndrome, and illustrates the diagnostic value of multi-tissue molecular analysis and functional validation in confirming pathogenicity.

12:35, EXPANDING THE PHENOTYPIC SPECTRUM OF GLI3-RELATED DISORDERS: ATYPICAL GREIG CEPHALOPOLYSYNDACTYLY SYNDROME ASSOCIATED WITH A TRUNCATING GLI3 VARIANT

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Background:
Pathogenic variants in *GLI3*, a key transcriptional mediator of the Sonic Hedgehog signaling pathway, are responsible for a spectrum of developmental disorders, including Greig cephalopolysyndactyly syndrome (GCPS). Classical GCPS is characterized by craniofacial anomalies, macrocephaly, hypertelorism, and polysyndactyly; however, phenotypic variability has been recognized. We report a child with an atypical GCPS phenotype with a pathogenic truncating *GLI3* variant and dental developmental abnormalities.

Case Presentation:
A 5-year-old boy was referred for genetic evaluation because of multiple congenital anomalies. Clinical examination revealed asthenic facies, high forehead, apparently reduced biparietal diameter, downslanting palpebral fissures, retrognathia, and dysplastic prominent ears. Additional findings included scattered melanocytic nevi on the thorax and marked dental abnormalities, comprising enamel mineralization defects, incisal hypomineralization, and dental matrix anomalies. Limb examination was notable for bilateral syndactyly of the fourth and fifth fingers, bilateral syndactyly of the second and third toes, pes planovalgus, widened first interdigital spaces, and broad halluces. No congenital cardiac malformations were identified. Prenatal karyotyping revealed a normal male karyotype (46,XY). Family history was notable for adult-onset neoplasms and a distant relative with agenesis of the corpus callosum.

Methods and Results:
Whole-exome sequencing identified a heterozygous frameshift variant in *GLI3* (NM_000168.6:c.4141_4142del, p.Arg1381Glyfs*30), predicted to result in premature protein truncation and loss of normal transcriptional activity. The variant established the diagnosis of a GLI3-related developmental disorder within the Greig cephalopolysyndactyly spectrum. Notably, the patient lacked some of the classical manifestations of GCPS, including macrocephaly and preaxial polydactyly.

Conclusions:
This case illustrates the clinical heterogeneity of GLI3-related disorders and supports expansion of the GCPS phenotypic spectrum. The combination of syndactyly, distinctive craniofacial features, and dental developmental defects highlights the importance of considering GCPS in atypical presentations and contributes to a broader understanding of GLI3-associated phenotypic variability

12:45, HALLUX MACRODATTILIA AS A HALLMARK OF CNP-PATHWAY DISRUPTION: 3 CASE REPORTS

Francesca Crivellaro

Background: C-type natriuretic peptide(CNP)-related overgrowth syndromes are exceptional, with very few families reported in the literature. To this day, few mutations involving NPR-B and NPR-C receptors, as well as CNP ligand, increasing the activity of its signaling pathway, have been identified as causative of peculiar skeletal overgrowth pattern, involving mainly long bones and the first radius of hands and feet. As different genetic culprits involving the same molecular pathway, they present some common features but lack a complete phenotypical overlap. We report here two cases bearing novel mutations involving both *NPPC* and *NPR3* genes, causing respectively “Overgrowth syndrome with 2q37t” and “Boudin Mortier syndrome”, in the aim of widening their phenotypic description.

Case presentation: A five-year-old girl was referred to genetics for statural overgrowth and Marfanoid habitus from her youngest age, presenting an height +5DS, associated with peculiarly long halluces, generalized arachnodactyly and genu valgum due to severe tibial bowing. Born at term from uneventful pregnancy, her birth anthropometries where characterized by a length at 99° centile, given her weight and OFC in the medium range. She was early cared in orthopedics for rapidly progressing severe scoliosis and slipped femoral epiphyses, both of which required orthopedic intervention, constituting a major disability cause. After exclusion of metabolic anomalies and constitutional myopathies suspected for mild hypotonia and muscular fatigability, WGS revealed the presence of a balanced translocation involving 2q37, delineating a specific skeletal overgrowth syndrome, already described in 5 families worldwide. The pathophysiology of her skeletal/phenotypic characteristics resides in the loss of negative control executed by a non-coding sequence located nearby the breakage point, resulting in a hyperexpression of *NPPC* gene.

A second patient presented a less accentuated high stature, attaining +2.5DS at around 12 years old, with characteristic long halluces necessitating chirurgical reduction, and Marfanoid habitus. Skeletal survey did not demonstrate any severe vertebral involvement or long bone bowing. Genetic analyses revealed the presence of a biallelic loss-of-function mutation in *CNR3* gene, causing impaired NPR-C activity, leading to a reduced clearance of CNP. A similar

phenotype is present in her sister, harboring the same mutations. Thus far, only four articles describing altogether 5 patients bearing a loss-of-function mutation involving *NPR3* gene, have been issued delineating what is known as Boudin-Mortier syndrome.

Discussion: Our two families elucidates the clinical and radiological heterogeneity in these diseases, despite their common pathway disruption. Long great toes appears to be a common hallmark overlapping between syndromes, where severity of impaction appears to be of variable presentation.

Conclusion: In the era of pharmacological modulation of CNP pathway to treat genetic short stature (such as Vosoritide in achondroplasia), less is still known about constitutive overactivation or loss of negative regulation of this physiological signaling. Our case report underscores the importance of increased awareness of such genetic syndromes, so far sparsely described, that could lead to early diagnosis and appropriate management, thereby highlighting any future potential targeted therapy.

Session 6 - Structural variation and chromosomal imbalances

16:00, REVISITING RETT SYNDROME BY LONG-READ WHOLE GENOME SEQUENCING (LR-WGS)

Alessandra Renieri1,2,3, Simone Pesaresi 1,3, Antoine Dahine 1,3, Deborah Serena 1,3, Matilde Smeraldo 2, Mariapia Mordente2, Miriana Danelli2, Camilla Ruta2, Chiara Fallerini1,2,3, Francesca Ariani1,2,3, Caterina Lo Rizzo3, Anna Maria Pinto3, Stegania Bigoni 4, Chiara Narducci 5, Valeria Scandurra 5, Sabrina buoni 5, Salvatore grosso 6, Ilaria Meloni 1,3, Simone Furini 7

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With very rare exceptions, most cases of Rett syndrome are caused by de novo mutations in the MECP2 gene. When the MECP2 mutation segregates in familial cases, it occurs in males with neurodevelopmental disorders and females who are healthy carriers. Despite numerous

attempts by various international groups, no one has succeeded in identifying a characteristic episignature for Rett syndrome, unlike many other neurodevelopmental disorders.

We have analyzed approximately 40 cases of Rett syndrome, using the new Long-read whole genome sequencing (LR-WGS) technique (PromethION24 ONT). This technique allows us to detect, in a single sequencing run, point mutations (SNVs), triplet expansions (STRs), copy number alterations (CNVs), structural rearrangements (SVs), as well as epigenetic alterations with four methylation levels (mCG, hmCG, CA, hCA).

It has emerged that in many cases, in addition to the de novo mutation in the MECP2 gene, there is another either inherited or the novo variant in another neurodevelopmental gene (e.g., TRIO, GRIN1, GRIN2A, etc.). This may explain why cases are not clustered within a single episignature.

Furthermore, these results are consistent with the complex model of Rett syndrome genesis that I hypothesized more than 20 years ago and shared in a 2003 publication (1). This genetic complexity is relevant for the appropriate management and therapy of Rett girls.

1) Renieri A, Meloni I, Longo I, Ariani F, Mari F, Pescucci C, Cambi F. Rett syndrome: the complex nature of a monogenic disease. J Mol Med (Berl). 2003 Jun;81(6):346-54. doi: 10.1007/s00109-003-0444-9. Epub 2003 May 16. PMID: 12750821.

16:15, TRAPPC9-RELATED INTELLECTUAL DEVELOPMENTAL DISORDER: A NOVEL CASE WITH CRYPTIC STRUCTURAL VARIANTS RESOLVED BY OPTICAL GENOME MAPPING

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Background: Autosomal recessive intellectual developmental disorder-13 (MRT13; OMIM #613192) is a rare neurodevelopmental disorder caused by biallelic pathogenic variants in *TRAPPC9*, located at 8q24.3. Individuals with MRT13 typically present with moderate-to-severe intellectual disability, structural brain abnormalities, postnatal microcephaly, motor delay, and variable but recurrent dysmorphic features. Reported craniofacial findings include

round face, brachycephaly, low anterior hairline, synophrys, epicanthal folds, hypertelorism, broad or prominent nasal bridge, short or smooth philtrum, thin upper lip, and low-set or prominent ears. Most reported pathogenic variants are single-nucleotide variants (SNVs) or small insertions/deletions, followed by copy number variants (CNVs), whereas the contribution of complex structural variants (SVs) remains poorly characterized. **Case report:** We report an Italian male with global developmental delay and moderate intellectual disability. Cognitive assessment performed at 5 years showed a WPPSI full-scale intelligence quotient of 50. Physical examination at 6 years revealed a height of 126 cm (+1.2 SDS) and weight of 55 kg (+3.86 SDS), with normocephalic head circumference. Dysmorphic features included turricephalic skull shape, epicanthal folds, low-set ears, and lateral sparseness of the eyebrows. Brain MRI demonstrated peritrigonal hyperintensities within the corona radiata. A familial chromosomal rearrangement was known from the diagnostic workup of the proband's younger sister, who carried an unbalanced translocation with terminal 4q34.3–q35.2 deletion and 8q24.3 duplication. Subsequent parental karyotyping revealed a reciprocal balanced translocation t(4;8)(q34.3;q24.3) in the father, while maternal karyotype was normal. In the proband, first-tier testing, including 60K array-CGH and trio-based WES, did not identify causative CNVs or SNVs. Subsequent 400K-resolution array-CGH detected a 31–39 kb microdeletion at 8q24.3 involving *TRAPPC9*, below the detection limit of the 60K and 180K platforms. Given the phenotypic concordance with MRT13 and the paternal translocation involving the chromosomal region of *TRAPPC9,* a pathogenic rearrangement affecting the paternal *TRAPPC9* allele was hypothesized, and explored through OGM. The trio-OGM analysis, combined with Paired-End WGS, refined the t(4;8) breakpoints, revealing disruption of *TRAPPC9* (NM_001160372.4) at 8q24.3 within intron 8, and confirmed a heterozygous ~35 kb deletion involving exons 10–12. These findings led to a final diagnosis of MRT13 in the proband. **Conclusions:** The identification of biallelic *TRAPPC9* disruption resulting from the combination of a small intragenic deletion and a balanced translocation expands the mutational spectrum of the disorder and emphasizes the importance of considering structural variants in unresolved neurodevelopmental cases. The integration of emerging genomic technologies, such as OGM, may significantly improve diagnostic yield and should be considered when conventional approaches fail to fully explain the clinical phenotype.

16:30, EXPANDING THE PHENOTYPIC SPECTRUM OF PALLISTER-KILLIAN SYNDROME: ADOLESCENT FOLLOW-UP OF A MILD FORM

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Background

Pallister-Killian syndrome (PKS) is a rare mosaic aneuploidy caused by tetrasomy of chromosome 12, usually due to a supernumerary isochromosome i(12p). The phenotype is highly variable and characterized by craniofacial dysmorphism, hypotonia, developmental delay, pigmentary abnormalities and multisystem involvement. Genotype-phenotype correlations remain complex because of tissue-specific mosaicism, also considering that attenuated forms are probably underdiagnosed and underreported in literature. Furthermore, data on clinical evolution in young adults are still limited. The aim of this study is to describe the clinical and neurodevelopmental follow-up of a patient with a relatively mild PKS phenotype up to 18 years of age, expanding knowledge on the syndrome's phenotypic variability and long-term evolution.

Methods

Patient's clinical, instrumental and genetic data from infancy to age of 18 years were retrospectively reviewed. PKS diagnosis was confirmed by array-CGH analyses on buccal mucosa cells. A literature review of PKS manifestations in young adults was also performed.

Results

Since early childhood, the patient presented with global developmental delay, hypotonia, marked motor and language delay, skin pigmentation anomalies and distinctive dysmorphic features: bitemporal narrowing, prominent forehead, hypertelorism, upslanting palpebral fissures, telecanthus, depressed nasal bridge, anteverted nares, long philtrum, prominent cupid bow, micrognathia, ear abnormalities, high palate, brachydactyly, interdigital webbing, nystagmus, strabismus and cryptorchidism. As he grew, micrognathia progressed to prognathia with coarsening facial features, while scoliosis and conductive hearing loss showed up. The neurocognitive profile was milder than in most cases reported in the literature, with functional verbal language, global cognitive functioning within the lower limits of normal and level 1 autism spectrum disorder, without epilepsy. Adolescent follow-up revealed severe progressive kyphoscoliosis surgically treated, progressive hearing loss, mild mitral insufficiency and the onset of tremors with parkinsonism-like features, still under evaluation. Peripheral blood standard karyotype and array-CGH revealing no alterations compatible with PKS and a 9p21.1 microdeletion involving the *LINGO2* gene, classified as a Variant of Uncertain Significance according to ACMG classification. The subsequent array-CGH analysis on buccal mucosa demonstrated the mosaic amplification of the entire short arm of chromosome 12, confirming PKS.

Discussion and Conclusions

This report expands the phenotypic spectrum of PKS by documenting a relatively mild form surviving into late adolescence and its evolution with aging. The orthopedic, audiological and neurological progression observed highlights the need for prolonged multidisciplinary follow-up and further studies in adolescent and adult cohorts. Of particular interest is the occurrence of tremors with parkinsonism-like features. While movement abnormalities have been reported in other chromosomal aneuploidies, no PKS patient with a documented movement disorder has been reported to date. In conclusion, this report also emphasizes the importance of maintaining clinical suspicion for PKS in mildly affected patients to select the most appropriate tissue and genetic testing for detecting mosaic tetrasomy 12p.

16:40, NEURODEVELOPMENTAL AND BEHAVIORAL FEATURES IN 48,XXYY SYNDROME: A CASE REPORT

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A 57-year-old male was referred to the Human Genetics Department for evaluation of moderate intellectual disability, aggressive behaviour, tall stature, facial dysmorphism, and severe sensorimotor axonal peripheral polyneuropathy. His medical history was notable for hypertension, type 2 diabetes mellitus, gastroduodenitis, diffuse hepatic steatosis, chronic peripheral venous insufficiency, compulsive traits, and addictive behaviours.

Physical examination revealed an elongated face, hypertelorism, facial asymmetry, a long philtrum, thin upper lip, large ears, shoulder girdle asymmetry, gynaecomastia, hyperkyphosis, flattening of the lumbar lordosis, osteoarthritic changes of the fourth and fifth fingers, left-sided Dupuytren's contracture, and lower-limb stasis dermatitis. Additional investigations showed hepatosplenomegaly, nodular adrenal lesions, and ischaemic leukoencephalopathy.

SNP-array analysis identified complete duplication of both the X and Y chromosomes, subsequently confirmed by conventional karyotyping, establishing the diagnosis of 48,XXYY syndrome.

48,XXYY syndrome is a rare sex chromosome aneuploidy affecting males and is associated with a broad and variable phenotype. Common manifestations include tall stature, delayed motor and speech development, learning difficulties, hypogonadism, behavioural and social difficulties, and variable neurodevelopmental impairment. Intellectual functioning is typically

within the borderline to mild intellectual disability range, although greater impairment may occur in selected cases.

This case illustrates the complex neurodevelopmental and multisystem phenotype associated with 48,XXYY syndrome. The presence of moderate intellectual disability and severe behavioural disturbance raises the question of whether the neurodevelopmental phenotype is attributable solely to the sex chromosome aneuploidy or whether it reflects a multifactorial process, potentially influenced by adverse social circumstances, limited early neurodevelopmental stimulation, and/or an additional genetic contributor.

16:50, DE NOVO INTERSTITIAL 3P21.31P14.3 DUPLICATION IN A BOY WITH ESOPHAGEAL ATRESIA, TALIPES EQUINOVARUS, HYPOTONIA, AND GLOBAL DEVELOPMENTAL DELAY

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Background: Copy number gains of the proximal short arm of chromosome 3 are rare. The classic duplication 3p syndrome involves the distal segment from 3p21 toward the telomere, whereas the interstitial region between 3p21.31 and 3p14.3 has been characterized almost exclusively through deletions. To our knowledge, an interstitial duplication confined to this proximal segment has not been reported.

Case presentation: We describe a boy aged 13 months. The pregnancy was complicated by intrauterine growth restriction, prompting emergency cesarean delivery at 35 weeks and 5 days, followed by a prolonged neonatal course with 9 days of intubation and 21 days of intensive care. He had esophageal atresia and bilateral talipes equinovarus treated with serial casting and orthotic footwear. Examination revealed generalized hypotonia and global developmental delay, with head control at 11 months, absent independent sitting, and emerging babbling. Dysmorphic features included brachycephaly, low-set ears, synophrys, a prominent forehead, a bulbous nasal tip, overlapping toes, and bilateral single transverse palmar creases. Chromosomal microarray identified a *de novo* duplication at chr3:46,408,373 to 58,539,343 (hg38), a gain of approximately 12.1 Mb spanning 3p21.31 to 3p14.3 and encompassing 248 genes, including several with established haploinsufficiency-related phenotypes, such as *SETD2, PTH1R, QRICH1*, and *BAP1*. Whole exome sequencing was unremarkable. The duplication was absent from population structural variation databases, and no triplosensitive gene or region within the interval has been curated to date. Two larger

overlapping duplications recorded in DECIPHER remain unclassified, one of which was reported with intellectual disability and microcephaly.

Conclusion: This *de novo* duplication does not overlap previously reported 3p gains and represents the near reciprocal of the recently described 3p21.31p14.3 deletion. The case expands the genomic and phenotypic spectrum of proximal 3p imbalances and underscores the interpretive challenge of gene-rich gains lacking established triplosensitivity.

17:00, INTRAFAMILIAL PHENOTYPIC VARIABILITY IN TWO SISTERS WITH PARTIAL TRISOMY 13Q31.1–Q34 AND TERMINAL 3P26.3 DELETION DUE TO MATERNAL BALANCED T(3;13)

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Background: Partial trisomy 13q is a rare chromosomal abnormality associated with developmental delay, intellectual disability, craniofacial dysmorphism, ocular anomalies, polydactyly, and congenital malformations. Terminal 3p deletions are additionally linked to neurodevelopmental impairment. Familial unbalanced rearrangements involving chromosomes 3 and 13 are exceptionally rare.

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Methods: Clinical and dysmorphological evaluation, pedigree analysis, conventional were performed in both siblings and family members. Molecular karyotyping (SNP-array) was performed in 2026 for diagnostic refinement.
Results: The younger sister was first evaluated in 2018 at 8 months of age because of developmental delay, strabismus, and postaxial polydactyly. Examination revealed craniofacial dysmorphism, smaller left eye, sacral dimple, increased lumbosacral hair growth, and right-sided postaxial polydactyly of both hands and right foot. Conventional karyotyping demonstrated 46,XX,add(3)(p25). She was re-evaluated in 2026 following epilepsy diagnosis and due to the need for more precise genomic characterization. The older sister was also evaluated in 2018 because of developmental delay and dysmorphic features, with the same conventional karyotype result. She underwent repeat genetic evaluation in 2026 for diagnostic refinement. Clinically, she had mild intellectual disability, recurrent urinary tract infections, urinary and fecal incontinence, megacolon, strabismus, pectus excavatum, and pes planovalgus. Chromosomal microarray analysis performed in 2026 identified the same imbalance in both sisters:

arr[GRCh37] 3p26.3(61495_2304111)x1,13q31.1q34(79999716_115103529)x3, corresponding to a terminal 3p26.3 deletion (~2.2 Mb) and pathogenic 13q31.1–q34 duplication (~35.1 Mb); 46,XX,der(3)t(3;13)(p26;q31). Family studies demonstrated balanced reciprocal translocation t(3;13)(p26;q31) in the mother and brother.
Discussion: Both sisters demonstrated overlapping dysmorphic and neurodevelopmental features with variable phenotypic severity despite identical genomic imbalance. The younger sister had more pronounced congenital anomalies, epilepsy, and polydactyly, whereas the older sister showed milder dysmorphism with urinary tract and gastrointestinal involvement. The phenotype is consistent with previously reported distal partial trisomy 13q cases. The additional terminal 3p26.3 deletion may further contribute to neurodevelopmental manifestations.
Conclusion: This familial case is consistant with the phenotypic spectrum associated with distal partial trisomy 13q and terminal 3p deletion due to familial balanced t(3;13). Despite identical genomic imbalances, the sisters demonstrated variable phenotypic severity.

Session 7 - prenatal diagnosis

17:10, COMPLEX GENETIC ANALYSIS IN ROUTINE PRENATAL PRACTICE – PRESENTATION OF INTERESTING CASES

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Prenatal genetic testing after invasive procedures has been implemented as a routine diagnostic and includes almost all techniques used in postnatal diagnostics. Detection of rare genetic conditions during pregnancy allows to better inform patients and doctors and provides important information for better medical care and possible treatments during pregnancy, delivery and after birth.

We present interesting cases from routine prenatal analysis after chorionic villus sampling or amniocentesis from our prenatal genetic laboratory. Genetic analyses include karyotyping, detection of copy number variants and exome/ trio exome sequencing. We will report on the specific genetic findings and their relevance in pregnancy. We also discuss the pros and cons of reporting pathogenic variants as well as variants of unknown significance

In view of rapid development of genetic knowledge and technologies, care providers must constantly evaluate medical decision making in pregnancy and after birth. Decision making processes must involve interdisciplinary teams, including gynaecologists, pediatricians, radiologists, geneticist and others. Due to the growing complexity of medical knowledge, there is a growing need for genetic counselling of patients with abnormal genetic test results.

17:25, PRENATAL DIAGNOSIS OF A DE NOVO 7Q11.21Q21.3 INTERSTITIAL DELETION IN A FETUS WITH A SEVERE SKELETAL DYSPLASIA-LIKE PHENOTYPE AND MULTIPLE CONGENITAL MALFORMATIONS

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Interstitial deletions involving the long arm of chromosome 7 are rare genomic rearrangements associated with highly variable phenotypes, including developmental delay, growth restriction, craniofacial dysmorphisms, limb anomalies, and multisystem congenital malformations. However, severe prenatal skeletal manifestations mimicking lethal skeletal dysplasias or fetal akinesia sequences have only rarely been described in association with proximal 7q deletions.

We here report the case of a non-consanguineous couple referred for prenatal genetic counselling at 20 weeks of gestation because of severe fetal growth restriction and suspected skeletal dysplasia. Pregnancy had been achieved through IVF after infertility. First trimester screening showed intermediate risk for trisomy 21, whereas non-invasive prenatal testing was low-risk for common aneuploidies.

Second trimester ultrasound examination revealed fetal biometry below the 5th percentile, severe thoracic hypoplasia, micromelia, frontal bossing, persistent hyperextension of the head, suspected lumbar lordosis, shortening of all long bones and multiple joint contractures, raising the suspicion of a severe skeletal dysplasia or fetal akinesia sequence. Due to the severe phenotype the couple opted for interruption of pregnancy.

Prenatal genetic investigations were performed on amniocytes and fetal tissue, including fetal karyotype, and array-CGH. Conventional cytogenetic analysis identified an abnormal male

karyotype: 46,XY,del(7)(q11q21). Array-CGH performed confirmed a *de novo* 32 Mb deletion at 7q11.21q21.3(63000288_95152730)x1, encompassing 261 OMIM genes, including 158 disease-associated genes.

Post-termination dysmorphological examination showed scoliosis, low-set ears, retronuchal pterygium-like anomalies, malar hypoplasia, severe microretrognathia, high-arched palate with cleft soft palate, bifid nasal tip, camptodactyly, clinodactyly, bilateral syndactyly, right rocker-bottom foot, and fixed flexion contractures involving both upper and lower limbs.

Although proximal 7q deletions have previously been associated with craniofacial dysmorphisms, developmental impairment, and limb abnormalities, the marked skeletal involvement observed in our fetus, including severe thoracic hypoplasia, arthrogryposis-like contractures, fetal akinesia features, and possible hydrops fetalis, appears unusually severe and expands the currently recognized prenatal phenotype associated with large 7q11.21q21.3 deletions.

17:35, MOLECULAR AND CLINICOPATHOLOGIC INSIGHTS FROM A FATAL CASE OF CONGENITAL GIANT HEPATIC HEMANGIOMA HARBORING A SOMATIC GNAQ P.GLN209PRO VARIANT

Congenital hemangioma is a rare vascular tumor that develops during fetal life, results fully formed at birth, and undergoes changes postnatally. The benign lesion's natural history is well-documented, typically resolving or stabilizing, although cases of persistent, unchecked growth have rarely been reported. We report a case of a prenatal detection of an abdominal mass at 33 weeks of gestation, responsible for a quick clinical worsening of a female newborn after the expansion of a hepatic hemangioma. An urgent surgical intervention was indicated but could not be performed because of premature exitus. Molecular screening for somatic activating variants in FFPE of affected tissue revealed low mosaicism for a recurrent GNAQ variant at the 209 amino acid position. Integrated molecular dynamics modeling and comparative case review substantiate the pathogenic role of the variant (see Figure 1) . Considering the severity of the congenital malformations and the identification of a potentially targetable molecular signature, this case underscores the critical importance of implementing a multidisciplinary approach including molecular characterization.

17:45, PRENATAL DIAGNOSIS OF A PATERNALLY INHERITED FEINGOLD SYNDROME: INTRA-FAMILIAL VARIABILITY AND COMPLEX CHROMOSOMAL REARRANGEMENTS

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Feingold syndrome (FS) is a rare autosomal dominant disorder characterized by mild facial dysmorphism, digital anomalies, microcephaly, growth delay, learning disability, and congenital malformations, most commonly gastrointestinal atresia. Type 1 Feingold syndrome (FS1) is caused by loss-of-function variants in the *MYCN* gene or deletions of 2p24 encompassing *MYCN*, and it's associated with variable expressivity.

We report a case identified during a second spontaneous pregnancy with a low risk combined test for aneuploidies. Second-trimester ultrasound revealed fetal growth restriction and oligohydramnios. Amniocentesis followed by array-CGH detected a heterozygous 5.3 Mb microdeletion at 2p24.3–p24.1, including *MYCN*, consistent with a diagnosis of FS1.

Parental studies identified a smaller 3.5 Mb deletion in the father at 2p24.2–p24.1, not involving *MYCN*. The father exhibited mild features suggestive of FS, including subtle facial dysmorphism, but lacked digital anomalies, microcephaly, growth delay, or intellectual disability.

The pregnancy was terminated at 22 weeks of gestation. Post-mortem examination confirmed the diagnosis of FS1, revealing anthropometric parameters at the lower limits of normal, characteristic facial dysmorphism, brachymesophalangy of the hands, syndactyly and brachydactyly of the toes, and renal hypoplasia.

Further investigations, including trio whole-genome sequencing and locus-specific FISH analysis, uncovered a complex chromosomal rearrangement in the father. In particular, the chromosomal region containing *MYCN*, deleted in the fetus, was found to be translocated to the short arm of chromosome 4, within a gene-poor heterochromatic region. This rearrangement may explain the father's mild phenotype, possibly due to reduced functional expression of the translocated *MYCN* allele.

This case highlights how complex structural rearrangements can result in distinct functional consequences at the same critical locus. The discrepancy between the fetal and paternal genomic alterations suggests a different pathogenic mechanism, likely related to positional effects, or altered gene regulation. These findings underscore the importance of integrating detailed phenotypic assessment with cytogenomic and advanced genomic analyses in prenatal diagnosis. Moreover, identifying complex chromosomal rearrangements has

significant implications for genetic counselling and recurrence risk assessment in future pregnancies.

Friday 18 September

Session 8 - Epigenetics

9:00, THE VALUE OF EPIGENETIC SIGNATURES AS KEY TO DIAGNOSIS IN NEURODEVELOPMENTAL DISORDERS

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Introduction : Despite advances in genetic testing strategies, approximately half of patients with neurodevelopmental disorders (NDDs) remain without a molecular diagnosis in sequence-based testing. However, for an increasing number molecularly confirmed NDDs specific DNA methylation signatures have been identified. Analysis of epigenetic signatures can provide an additional diagnostic layer in unresolved patients.
Methods : Genome-wide methylation profiling and analysis by EpiSign™ software was applied to a cohort of > 500 patients with unexplained developmental delay or variants of uncertain significance (VUS) in genes potentially associated with epigenetic regulation. Validation was performed using 60 positive control samples representing 53 known syndromes.
Results : The analysis yielded clinically relevant findings in approx. 5% of previously unresolved cases; in several cases the diagnosis could be confirmed by re-assessment of the exome data, other patients could be confirmed clinically. In cases with variants of uncertain significance, detection of a matching episignature supported reclassification as likely pathogenic, directly influencing clinical interpretation and patient management.
Conclusion: In conclusion, epigenetic methylation signature profiling represents a valuable complementary tool for the diagnosis of neurodevelopmental disorders, particularly in cases with negative or uncertain genomic findings. Integration of episignature analysis into clinical diagnostic workflows increases diagnostic yield and contributes significantly to variant classification in rare disease genetics.

9:15, PHENOTYPIC AND DNA METHYLATION SIGNATURE VARIABILITY IN FAMILIAL RUBINSTEIN-TAYBI SYNDROME

Quentin Sabbagh, Amantine Santini, Samuel Fennelly, Camille Charbonnier, Florence Demurger, Alice Goldenberg, Sarah Grotto, Marie-Line Jacquemont, Gwenaëlle Lancelot, Marine Legendre, Pauline Marzin, Gaël Nicolas, Clément Sauvestre, Elise Schaefer, Didier Lacombe, Patricia Fergelot, **Julien Van Gils***

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Background

Rubinstein-Taybi syndrome (RTS) is a rare Mendelian disorder of the epigenetic machinery caused by pathogenic variants in *CREBBP* (RTS1) or *EP300* (RTS2), encoding histone acetyltransferases critical for chromatin dynamics. While RTS predominantly arises de novo, familial transmission remains exceptionally rare and poorly characterized.

Methods

Here, we present the first comprehensive case series of familial RTS, comprising 13 affected individuals in five unreported families (four *CREBBP*-related, one *EP300*-related) with detailed clinical, molecular, and epigenetic characterization.

Results

We identified five transmitting parents and eight affected offspring carrying four distinct (likely) pathogenic variants: two *CREBBP* missense variants—p.(Phe1632Val), shared by two families, and p.(Tyr1167Cys)—one *CREBBP* nonsense variant—p.(Gln2200Ter)—and one *EP300* frameshift variant—p.(Ser552LeufsTer65). Clinical assessment revealed milder phenotypes in transmitting parents compared to offspring, with reduced penetrance of developmental disorder (4/5 vs. 8/8), intellectual disability (2/5 vs. 4/7), and distal limb abnormalities. Structural modeling predicted destabilizing effects for both *CREBBP* missense variants (FoldX ΔΔG > 2.4 kcal/mol), alongside strong conservation and damaging *in silico* predictions, supporting their pathogenicity.

Discussion

Genome-wide DNA methylation (DNAm) array analysis of blood-derived DNA in parent-offspring pairs confirmed variant pathogenicity through RTS-specific episignatures in all families compared to healthy controls and revealed distinct *CREBBP* and *EP300* DNAm profiles. Despite demonstrable intrafamilial variability, episignatures remained reproducible across generations, while age emerged as a significant modifier of DNAm profiles. These findings validate DNAm signatures as reproducible diagnostic tools while demonstrating that identical pathogenic variants generate intrafamilial episignature variability, offering a potential molecular framework to decipher phenotypic heterogeneity in familial rare diseases.

9:30, DNA METHYLATION SIGNATURES DRIVE MOLECULAR DIAGNOSIS IN GENETICALLY UNSOLVED MENDELIAN DISORDERS OF THE EPIGENETIC MACHINERY

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13 Montpellier University Hospital, Department of Medical Genetics, Montpellier, France.
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Background/Objectives

Mendelian disorders of the epigenetic machinery (MDEM) represent a clinically recognizable group of rare diseases caused by pathogenic variants in genes regulating chromatin dynamics. Despite the widespread implementation of NGS, a significant proportion of individuals with suspected MDEM remain genetically unsolved after standard-of-care (SoC) testing. DNA methylation (DNAm) signatures have emerged as a powerful biomarker in rare disease diagnostics, yet their positive predictive value (PPV) in genetically unsolved individuals has not been systematically evaluated in a clinically homogeneous setting.

Methods

We applied DNAm signature analysis to 14 individuals with clinically suspected MDEM left genetically unsolved by SoC testing—at minimum chromosomal microarray and MDEM gene panel sequencing. Each conclusive episignature result was followed by a systematic post-episignature genomic workup, including long-read genome sequencing, exome sequencing, and/or visual reinspection of BAM files, to independently seek molecular confirmation in the episignature-predicted gene.

Results

A conclusive episignature was identified in 6 of 14 individuals (42.9%), comprising five without a potentially causative SoC variant and one harboring an inherited *CHD7* variant of uncertain significance (VUS). Post-episignature investigations retrospectively unmasked a pathogenic variant in the DNAm signature-predicted gene in all five individuals, demonstrating a PPV of 100%. Molecular resolution occurred through three distinct mechanisms: SoC calling failure in *KMT2D* (*n* = 3)—including a pathogenic 5'UTR variant causing uORF-mediated haploinsufficiency, a 32-base pair exon deletion, and an *Alu*Y exonic insertion missed by standard bioinformatic pipelines—causal variants in *SIN3A* (*n* = 1) and *TRRAP* (*n* = 1) absent from the SoC gene panel at the time of initial testing, and episignature-driven reclassification of the inherited *CHD7* VUS as pathogenic.

Conclusions

These findings provide a rigorous real-world evaluation of DNAm signature PPV in a clinically homogeneous rare disease setting and demonstrate the clinical utility of episignature-driven diagnostic strategies—both for diagnosis rescue in genetically unsolved individuals and for functional reassessment of variants of uncertain significance. They further advocate for the broader clinical implementation of DNAm signature analysis across rare disease diagnostics.

9:45, UTILITY OF EPISIGNATURE ANALYSIS IN CLINICAL GENETICS AND A POTENTIAL NOVEL ASSOCIATION OF TLK2 GAIN-OF-FUNCTION WITH SYNDROMIC NEURODEVELOPMENTAL DISORDER

Cord-Christian BECKER [1], Asuman KOPARIR [2], Kerstin KAMOLANE [3], Eva METZGER [3]

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Introduction

In clinical genetic care for rare diseases, sequence-based genetic diagnostics currently achieve a diagnostic yield of approximately 40–50%. However, important limitations remain, including technical blind spots such as deep intronic variants that may escape exome sequencing or repeat expansions that are difficult to detect using short-read technologies. Furthermore, the interpretation of variants of uncertain significance (VUS) continues to represent a major diagnostic challenge.

Meanwhile, genome-wide DNA methylation profiling is emerging as a complementary diagnostic tool to address these challenges for certain disease entities. Characteristic DNA methylation episignatures have been identified for more than 100 genetic disorders. Published data show that comprehensive genome-wide DNA methylation analysis identifies disease-specific episignatures in 9–18.7% of tested individuals and contributes an additional diagnostic yield of approximately 4% beyond conventional genetic testing. In targeted diagnostic settings diagnostic confirmation through episignature detection helps to resolve unclear cases in more than 30%.

Methods

Comprehensive episignature analysis was integrated into the diagnostic workflow of patients with unresolved phenotypes, inconclusive molecular findings, or variants of uncertain significance. Results were interpreted together with clinical and genomic data.

Results

Case presentations demonstrate how epigenomic profiling complements conventional sequence-based genetic testing. For example, in several of our patients, variants of uncertain significance could be reclassified as likely pathogenic (ACMG class 4) based on episignature diagnostics using the PS3_st criterion. Consequently, these patients received (probable) molecular diagnoses.

Furthermore, in another patient carrying a 17q23.2 duplication, we identified potential evidence for a novel genotype–phenotype association involving gain-of-function alterations of the *TLK2* gene. Loss-of-function variants in *TLK2* are known to cause TLK2-related neurodevelopmental disorder (OMIM #618050), for which a characteristic episignature pattern has previously been established. In our patient, episignature analysis demonstrated

a mirrored episignature pattern compared to the shift observed between normal controls and individuals with loss-of-function variants in TLK2.

Discussion & Conclusion

Episignature diagnostics help resolve an additional proportion of previously unsolved cases. At the same time, they raise new questions, as illustrated by our case of a *TLK2* duplication associated with a potentially corresponding, previously undescribed episignature pattern. Further patients carrying functionally similar alterations will be required to confirm this possible association.

10:00, THE UTILITY OF EPIGENETIC SIGNATURE ANALYSIS IN THE EVALUATION OF VARIANTS OF UNCERTAIN SIGNIFICANCE (VUS) AND FOR THE MOLECULAR CONFIRMATION OF GENETIC DIAGNOSES

Antje Kampmeier[1], Tobias Bartholomaeus[2], Stefanie Beck-Wödl[3], Jasmin Beygo[1], Christel Depienne[1], Juliane Eckhold[1], Marc-Alexander Gose[1], Tobias B Haack[2], Fabian Kilpert[1], Kevin Luethy[1], Lara Kimmig[1], Teresa Neuhann[2], Ilaria Parenti[1], Harald Surowy[1], Christopher Schroeder[1], Sandra Ueberberg[1], Frank Kaiser[1], Alma Kuechler[1]

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Variants of uncertain significance (VUS) pose a major challenge in determining the genetic cause of developmental disorders (DD) and intellectual disability (ID). Additional diagnostic approaches are often required to clarify their clinical relevance. For a growing number of disorders, disease-specific DNA methylation patterns (epigenetic signatures, episignatures) have been identified, providing a valuable tool for VUS classification.

We applied episignature analysis to further characterize VUS identified in five genes across four individuals with DD/ID. In individual 1, the episignature profile showed high-confidence concordance with *UBE2A*-related intellectual disability type Nascimento. In individual 2, the profile was consistent with *KDM6A*-related Kabuki syndrome. Integrating episignature data with bioinformatic variant interpretation and clinical phenotype allowed both variants to be reclassified as likely pathogenic, thereby establishing the genetic diagnoses. In individual 3, carrying one VUS in *KMT2A* and one in *NIPBL*, episignature analysis did not yield conclusive results. Thus, the diagnosis remained unclear. In individual 4, a VUS in *KANSL1* could be reclassified as likely benign based on epigenome, segregation and detailed genomic analysis of this locus.

Individual 5 presented with typical clinical phenotype of CHARGE syndrome, but exome sequencing failed to identify any pathogenic variant in *CHD7*. Analysis of the epigenetic

signature finally revealed with high confidence a *CHD7*-typical epigenetic signature, and genome sequencing identified an intronic variant in *CHD7*. Thus, the clinical diagnosis could be molecularly confirmed.
In Conclusion, we report on five individuals with developmental disorders and intellectual disabilities in whom episignature analysis was used to clarify VUS or to confirm a clinical diagnosis. In three cases, this approach enabled a definitive genetic diagnosis. Our results underscore the clinical utility of episignatures as a complementary tool for interpreting VUS or identifying the molecular genetic cause when a clearly defined disease-specific methylation pattern is present.

10:15, THE DIAGNOSTIC COMPLEXITY OF CREBBP GENE: A CLINICAL CASE AT THE PHENOTYPIC BOUNDARY BETWEEN MENKE-HENNEKAM AND RUBINSTEIN-TAYBI SYNDROMES

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Pathogenic variants in the *CREBBP* gene have long been associated with Rubinstein-Taybi syndrome type 1 (RSTS1). It was only in 2016 that Menke et al. first described a clinically distinct phenotype arising from variants in exons 30–31 of the same gene, in individuals lacking the hallmark features of RSTS1, later formally recognized as Menke-Hennekam syndrome type 1 (MRHS1, OMIM #618332). Despite this separation, the boundary between the two conditions remains incompletely defined, particularly for atypical variants in this shared genomic region.

We report a 4-year-old male, firstborn to non-consanguineous parents, presenting at birth with symmetric intrauterine growth restriction (birth weight 2350 g, <3rd centile), distinctive facial dysmorphisms and neonatal recurrent desaturation episodes requiring intensive care admission. Extensive workup including cerebral, cardiac, pulmonary, and abdominal imaging was unremarkable, and newborn metabolic screening was negative. Follow-up revealed

psychomotor delay. Chromosomal microarray (array-CGH, 130 kb resolution) showed a normal male profile with no copy number variants. Trio clinical exome sequencing identified a de novo heterozygous frameshift variant in *CREBBP* (exon 31): c.6116_6117delTG, p.(Val2039Aspfs*301), classified as likely pathogenic per ACMG criteria. The variant's location in exon 31 places it within the genomic region shared by both conditions, and the patient's phenotype reflects this ambiguity: facial features are only partially consistent with RSTS1 and partially overlapping with MRHS1, suggesting either a genuine phenotypic intersection or an atypical presentation irresolvable by clinical criteria alone. Frameshift variants in this region remain underrepresented in the literature, further limiting genotype-phenotype interpretation. An episignature methylation analysis specific for Rubinstein-Taybi syndrome has been requested and is currently being processed at Bambino Gesù Children's Hospital in Rome; results are pending. This case underscores the diagnostic complexity at the *CREBBP* exon 30–31 locus and supports the emerging role of episignature analysis as a molecular discriminator between these two recently separated syndromic entities.

Session 9

11:45, COMPOUND HETEROZYGOUS VARIANTS IN PAICS SUMMARIZE THE DIVERGENT PREVIOUSLY DESCRIBED PHENOTYPES

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Biallelic variants in *PAICS*, one of the ten genes involved in the de novo purine synthesis (DNPS), were originally associated to an extremely rare phenotype with multiple and severe congenital abnormalities, such as polyhydramnios due to esophageal atresia, congenital heart disease and urogenital anomalies, which resulted lethal in the first days of life. Vertebral and limb defects and distinctive craniofacial features were also described. To date, three patients with these clinical characteristics but with no neurologic involvement have been described in the literature.

More recently, two siblings with none of these features but with a severe neurodevelopmental phenotype with regression and ocular involvement have been reported.

We describe a new patient with two compound heterozygous variants in the PAICS gene, p.Ser35Phe and p.Cys281Ter, born with multiple congenital malformations overlapping those of the originally described siblings: esophageal atresia, lung hypoplasia, vertebral anomalies, cryptorchidism, short stature and dysmorphic facial features. He also had developmental delay, epilepsy never occurred.

The features presented by our patient and the relatively longer period of follow up allowed us to detect in a single patient almost all the features previously described in different families.

11:55, NAMING THE ILLNESS: THE LONG ROAD FROM CLINICAL SIGNS TO MOLECULAR DIAGNOSIS

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Aarskog-Scott Syndrome (AAS) is a rare developmental disorder characterized by facial, limbs and genital features, and a disproportionate acromelic short stature. The intellectual development of people with Aarskog-Scott syndrome varies widely. Most individuals with AAS have normal intelligence; however, some may have mild learning and -behavioral problems.

The majority of the clinical features in AAS can be ascribed to loss-of-function variants in the *FGD1* gene, located on the short arm of the X chromosome. This gene encodes a protein that acts as a Guanine nucleotide Exchange Factor (GEF) for Cdc42. The GEF activates Cdc42, participating directly in cytoskeletal organisation, growth regulation and normal embryonic development in mammals.

Alterated transmission of Cdc42 signals impairs normal development of bones and other tissues, resulting in the wide variety of abnormalities that occur in people with Aarskog-Scott syndrome.

Aarskog-Scott syndrome is inherited in an X-linked recessive pattern: affected males can inherit the variant from an unaffected or mildly affected carrier mother. In 10% of cases the disorder results of a *de novo* pathogenic variant

Here we present a novel patient with a clinical diagnosis of AAS, but with a long road to genetic diagnosis. He performed *FGD1* sequencing twice, both with Sanger sequencing and

NGS, with normal results. At this time, a Variant of Unknown Significance (VUS) in the *CBL* gene was detected, leading to an invasive follow up to prevent eventual complications such as juvenile myelomonocytic leukemia. Despite the low level of confidence based on the previous negative results, MLPA analysis was performed, revealing a deletion encompassing the entire exon 1 and thereby confirming the diagnosis.

Establishing the molecular cause of a genetic disorder is fundamental for validating the patient's experiences and supporting effective management of the condition. Furthermore, it reduces uncertainty and the possibility of misleading alternative diagnosis, which can bring to unnecessary and costly investigations, together with anxiety-inducing situations.

Keywords: Aarskog-Scott Syndrome, faciogenital dysplasia, X-linked recessive, MLPA, *FGD1*.

12:05, ONE VARIANT, THREE PHENOTYPES: 'VARIABLE EXPRESSIVITY OF A RECURRENT NSD2 VARIANT 'IN RAUCH–STEINDL SYNDROME

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Background: Rauch–Steindl syndrome (RAUST; OMIM #619695; ORPHA:659642) is an extremely rare autosomal dominant neurodevelopmental disorder caused by pathogenic variants in *NSD2*. To date, approximately 41 affected individuals have been reported in the literature, and Orphanet estimates its prevalence to be below 1 in 1,000,000. The phenotype partially overlaps with Wolf–Hirschhorn syndrome, although the classic "Greek warrior helmet" facial appearance and seizures are often absent. Core findings include prenatal and postnatal growth failure, microcephaly, developmental delay, and variable dysmorphic features.

Case presentation: We report a female child born to non-consanguineous parents after an in vitro fertilization pregnancy. Intrauterine growth restriction (IUGR) was detected from the 12th gestational week and persisted throughout pregnancy, with fetal growth lagging approximately five weeks behind gestational age. She was delivered vaginally at 37 weeks, with anthropometric parameters corresponding to approximately 32 weeks; birth weight was 1600 g and birth length was 41 cm. Postnatal growth failure and microcephaly persisted. At 14 months, weight was 5.2 kg (SDS −5.07), length 66 cm (SDS −3.95), and head circumference 40 cm (SDS −4.97). Dysmorphic examination revealed a mild, non-classic Greek warrior helmet-like gestalt, with triangular face, relative frontal prominence/frontal bossing, deep-set and large-appearing eyes, strabismus, narrow lower face, mild retrognathia, thin nasal

bridge, and mildly outwardly rotated ears (Fig.1). Developmental delay was most prominent in expressive language, whereas eye contact, response to name, social interaction, and joint attention were preserved. She walked independently during the second year of life and had no seizures. Neuroimaging showed nonspecific millimetric periventricular signal changes. Clinical exome sequencing identified a maternally inherited heterozygous pathogenic loss-of-function nonsense variant, NM_001042424.3:c.2263C>T; NP_001035889.1:p.(Arg755*), in the *NSD2* gene. The mother was only mildly affected, with short stature (approximately −2.3 SDS) and subtle dysmorphic features.

Discussion and conclusion: The recurrent *NSD2* variant c.2263C>T; p.(Arg755Ter) has previously been reported de novo in a male fetus with severe prenatal multisystem involvement, including IUGR, microcephaly, complex congenital heart malformation, cerebellar vermis hypoplasia, and pregnancy termination at 26+6 weeks (Zanoni et al., 2021). In our family, the same variant was associated with two additional phenotypic presentations: a child with prenatal-onset growth failure, microcephaly, and language delay, and a mildly affected mother with short stature and subtle dysmorphic features. This “one variant–three phenotypes” observation supports marked variable expressivity and a broad clinical spectrum of recurrent *NSD2* loss-of-function variants in Rauch–Steindl syndrome.

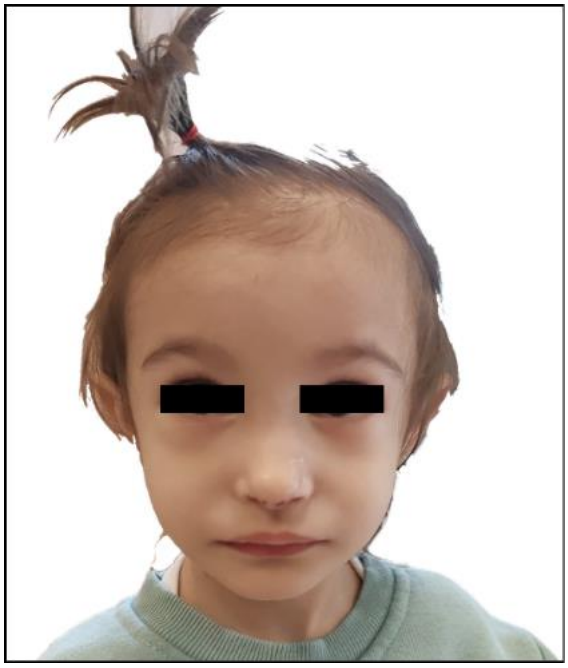

Fig. 1 Clinical photograph showing facial gestalt of the patient.

12:15, INTELLECTUAL DEVELOPMENTAL DISORDER, X-LINKED 99, SYNDROMIC (MRXS99F; OMIM#300968) AS AN EXAMPLE OF SYNDROMES WITH FEMALE-RESTRICTED PHENOTYPE.

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Background: The different number of X chromosomes in males and females, as well as the phenomenon of X chromosome inactivation, cause X-linked diseases to have a different course in males and females. Some genes escape X-inactivation. Moreover, the inactivation process is not always random. Therefore, interpreting the clinical significance of molecular variants in genes located on the X chromosome can be highly challenging.
In the OMIM database there are some disorders with a female-restricted phenotype (#300968; #301041; #301142; #300088). We are going to present an adult patient with *USP9X*-related female-restricted phenotype and briefly discuss the others.

Case Presentation: Currently 21-year-old female patient was referred to our Genetic Counseling Clinic almost 20 years ago due to abnormal speech and cognitive development, autism, failure to thrive, short stature, and dysmorphic features. Other medical problems: hypothyroidism, strabismus and astigmatism, bilateral hearing loss, mitral valve prolapse, epilepsy, chest deformity, scoliosis and joint contractures. Exome sequencing revealed the presence of a novel pathogenic molecular variant c.5458C>T p.(Arg1820*) in *USP9X* gene (NM_001039591.3) in a mosaic state (~23% in the tested tissue).

Discussion: *USP9X* is one of the genes that escape X-inactivation. Both males and females with pathogenic variants in the *USP9X* gene present with neurological symptoms, including global developmental delay, ID, hypotonia, motor and speech delay and brain abnormalities. Female-restricted phenotype (MRXS99F) also includes: hearing loss, ophthalmological abnormalities, renal, skeletal and heart defects. Female-restricted phenotype result from de novo heterozygous LOF mutations, while symptoms observed in males are due to missense variants with milder allelic impact (e.g. partial LOF), often maternally inherited.
Other female-restricted phenotypes include: *ZC4H2*-related Wieacker-Wolff syndrome (WRWFFR; #301041), *SLC9A6*-related neurodegenerative disorder with parkinsonism and cognitive impairment (NDPACX; #301142) and *PCDH19*-related developmental and epileptic encephalopathy 9 (#300088). Wieacker-Wolff syndrome also has an X-linked recessive form that manifests in males. Many affected females with NDPACX have male family members with the Christianson type of X-linked syndromic intellectual developmental disorder (MRXSCH; #300243). In *PCDH19*-related developmental and epileptic encephalopathy 9 carrier males are unaffected except for psychiatric/behavioral abnormalities.

Conclusions: When interpreting the significance of molecular variants in X-linked genes, we must consider not only the well-known scenarios (asymptomatic carrier status for X-linked recessive disorders in females; more severe manifestations in males and milder manifestations in females; or male lethality with symptoms observed only in females in X-linked dominant disorders), but also the possibility of distinct phenotypes depending on both sex and the type of molecular variant. Not all mechanisms underlying phenotypic differences between males and females are fully understood.
Partially funded by the project S207/2024.

12:25, A ROBIN REDBREAST IN A CAGE: A FATAL LAMINOPATHY IN A NEWBORN

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Background

Restrictive dermopathy is a rare, invariably lethal congenital laminopathy caused by biallelic ZMPSTE24 or LMNA variants, characterized by highly recognizable features and respiratory insufficiency.

Case history

We describe a female infant born at 32+1 weeks' gestation (SGA -3 SD) after preterm rupture of membranes. Severe respiratory distress at birth requiring difficult intubation at 11 minutes and subsequent mechanical ventilation. The infant displayed marked congenital anomalies included craniofacial dysmorphism, joint contractures, skin fragility with blistering, and poor tissue integrity including fragile vessels. Early suspicion of epidermolysis bullosa, but later clinical genetics consultation raised suspicion of restrictive dermopathy. Progressive management included escalating ventilatory support, diuretics for edema, and intensive multimodal analgesia/sedation for severe pain and handling intolerance due to skin fragility. Genetic testing confirmed homozygous ZMPSTE24 variant consistent with autosomal recessive restrictive dermopathy. After multidisciplinary discussion, ventilatory support was withdrawn on day 12; the infant died approximately 6 hours after extubation.

Conclusion

This case report illustrates a very rare condition with a highly recognizable phenotype, which may however be confused with other genetic dermatoses, leading to diagnostic delay.

12:35, PROGRESSIVE ARTHROPATHY REVEALING MUCOLIPIDOSIS IIIΓ: A PHENOTYPE-BASED GENOMIC DIAGNOSIS

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Introduction

Mucolipidosis III gamma (ML IIIγ) is an ultra-rare autosomal recessive lysosomal trafficking disorder caused by biallelic pathogenic variants in the *GNPTG* gene. ML IIIγ typically manifests in early childhood with progressive joint stiffness, flexion deformities of the fingers, restricted range of motion, connective tissue abnormalities and chronic pain. Due to its rarity and phenotypic overlap with rheumatologic and neuromuscular disorders, ML IIIγ may remain unrecognized in routine diagnostic pathways.

Methods

Detailed clinical phenotyping and phenotype-based analysis of trio genome sequencing (tGS; Modelproject Genome-Sequencing, MHH).

Results

We report on a 14-year-old boy who developed progressive fibrosing arthropathy with onset at five years of age. Initial manifestations consisted of bilateral contractures of the distal finger joints. Over time, increasing connective tissue proliferation around the joints resulted in progressive contractures involving both upper and lower extremities, particularly the fingers, wrists, elbows, and shoulder girdle. Biopsy and MRI showed indecisive inflammation and hypertrophy of the synovialis. A genetic cause was strongly suspected from the beginning, however, targeted genetic testing and trio-exome sequencing (tES) for rheumatologic/ autoinflammatory, neuromuscular disorders, and mucopolysaccharidosis remained inconclusive. Finally, tGS identified biallelic (likely) pathogenic variants in *GNPTG*, consistent with a diagnosis of Mucolipidosis III gamma, five years after initial genetic testing.

Conclusion

This case highlights that progressive contractures and fibrosing arthropathy are not exclusively indicative of rheumatologic or neuromuscular disease but may represent rare disorders such as ML IIIγ. Our findings emphasize the value of early implementation of phenotype-based tGS analysis, as it may substantially shorten the diagnostic process and

improve recognition of rare and underrecognized genetic diseases that can be missed by disease-specific diagnostic approaches.

12:45, A SEVERE NEONATAL FIBRILLINOPATHY CAUSED BY A DE NOVO FBN1 VARIANT: EXPANDING THE CLINICAL SPECTRUM

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FBN1 pathogenic variants are associated with a spectrum of connective tissue disorders, most notably Marfan syndrome and related fibrillinopathies. Fibrillin-1, a key structural component of the extracellular matrix, plays a critical role in multiple organ systems, particularly the cardiovascular, ocular, and skeletal systems. Variants affecting cysteine residues within the *FBN1* neonatal region (exons 24–32) are associated with neonatal Marfan syndrome, a severe early-onset phenotype, although the full phenotypic spectrum remains incompletely characterised.

We report a 2-year-old child who, at birth, presented with multiple congenital contractures, including involvement of the feet, knees, elbows, and hands, associated with arachnodactyly, retrognathia, micrognathia, and a high-arched palate, and suspected cardiopathy. He was admitted to the neonatal care unit for multidisciplinary evaluation. Based on these initial physical examination findings, an initial multigene panel for congenital arthrogryposis was performed which returned normal results. Given the severity and multisystemic nature of the presentation, the investigation was subsequently expanded to whole exome sequencing, which identified a *de novo* heterozygous *FBN1* variant (NM_000138.5:c.3095G>A; p.Cys1032Tyr, exon 26), currently classified as pathogenic.

During the neonatal admission and following multidisciplinary assessment, additional systemic manifestations became evident. Cardiac evaluation revealed redundant leaflets of the aortic, mitral, and tricuspid valves with mild regurgitation, redundant intracavitary tissue of the left atrium, a mobile septum primum, patent *foramen ovale* with left-to-right shunt, and aortic root dilation. Ophthalmological assessment identified bilateral lens subluxation, optic nerve abnormalities, and severe myopia (−15 diopters bilaterally). These findings were consistent with the diagnosis of neonatal Marfan syndrome.

Notably, this patient also developed a progressive progeroid appearance and was found to have a diaphragmatic hernia — both representing atypical features in the context of neonatal region *FBN1* variants. Progeroid fibrillinopathy has been consistently linked to variants in the 3' end of *FBN1* (exons 64–65), not to the neonatal region, making this finding unexpected. While diaphragmatic hernia has been occasionally reported in neonatal Marfan syndrome, it remains rare and has been associated with shorter survival. Together, these

findings suggest a potential expansion of the phenotypic spectrum associated with neonatal region *FBN1* cysteine variants.

This case highlights the diagnostic challenges posed by atypical fibrillinopathies, the importance of whole exome sequencing in severe neonatal presentations, and the need for long-term multidisciplinary surveillance in this population.

Session Phenotypic expansion or dual diagnosis?

14:00, MODIFIED FACIAL PHENOTYPE IN SYNDROMIC CHILDREN: A SOURCE OF DIAGNOSTIC UNCERTAINTY

Introduction: Facial dysmorphism plays a central role in the clinical recognition of genetic syndromes, with certain features considered highly characteristic or even pathognomonic. However, as affected individuals grow older, cosmetic or corrective interventions aimed at "normalizing" appearance may alter or obscure key phenotypic traits, thus complicating clinical assessment. We present two patients in whom cosmetic manipulations modified syndrome-defining features and contributed to diagnostic uncertainty.

Case Presentations: *Case 1:*A 24-year-old woman was evaluated for syndromic intellectual disability. She had a history of intrauterine growth restriction and was born via spontaneous vaginal delivery (46 cm, 1750 g). Postnatal failure to thrive was noted. She walked at 18 months and remains non-verbal, with severe intellectual disability (IQ 20–34). At examination: height 150 cm (<3rd percentile), weight 50 kg, head circumference 47.5 cm (<3rd percentile). Dysmorphic features included microcephaly, micrognathia, thick eyebrows, type A brachydactyly, and cone-shaped epiphyses of the phalanges. No relevant family history was reported. Cornelia de Lange syndrome (CdLS) and KBG syndrome were considered in the differential diagnosis. Notably, the patient had undergone multiple sessions of facial photoepilation, which initially obscured the presence of synophrys and high arched eyebrows, both key features suggestive of CdLS. Whole exome sequencing (WES) identified a heterozygous pathogenic variant in *HDAC8*, confirming CdLS.

*Case 2:*A 15-year-old girl was referred for global developmental delay and facial dysmorphism. She required incubator care for three months after birth. She walked at 3 years and spoke her first words at 6 years, currently using short sentences. She has high refractive error and surgically corrected strabismus. Family history was unremarkable. At examination: height 148 cm (<3rd percentile), weight 44 kg, head circumference 51 cm (microcephaly). Dysmorphic features included thick eyebrows, large upper central incisors, a single transverse palmar crease on one hand, and clinodactyly. KBG syndrome was suspected; however, the characteristic macrodontia had been modified through prior orthodontic treatment, reducing its clinical prominence and creating diagnostic hesitation. WES identified a heterozygous pathogenic variant in *ANKRD11*, confirming KBG syndrome.

Conclusion: These cases highlight an underrecognized diagnostic pitfall in clinical dysmorphology: cosmetic and corrective interventions may significantly modify or obscure characteristic facial features of genetic syndromes. Parents may not consider such interventions medically relevant and may omit them during history taking. In older patients especially, modified facial features may obscure classic phenotypic patterns, misdirect differential diagnosis, and prolong the diagnostic process. Review of childhood photographs can be invaluable in reconstructing the original phenotype and clarifying syndrome recognition.

14:10, SKIN PIGMENTATION DISORDERS AS A DOMINANT TRAIT IN PATIENTS WITH A PHENOTYPE SUGGESTING GENETIC PREDISPOSITION – AN ATTEMPT TO ELUCIDATE THE MOLECULAR BASIS: A CASE STUDY

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Skin pigmentation disorders (pigmentary disorders) comprise a group of conditions characterized by changes in skin coloration and rank among the most common dermatological diseases. These alterations are driven by various mechanisms, including those involving dysfunctional melanocytes and their regulatory factors.

Pigmentary disorders are observed in skin conditions presenting with:

Hyperpigmentation (hypermelanoses), including:

- Epidermal hypermelanoses: CALMs (café-au-lait macules), lentigines, freckles (ephelides), post-inflammatory hyperpigmentation (PIH)
- Dermal hypermelanoses: melanocytic nevi (congenital/acquired/others), erythema dyschromicum perstans
- Generalized hyperpigmentation

Hypopigmentation (hypomelanoses), including:

- Congenital: albinism, piebaldism, hypomelanosis of Ito, hypopigmented macules
- Acquired: vitiligo, leukoderma, pseudoleukoderma

Of note is the remarkable clinical heterogeneity and diverse etiology of skin pigmentation disorders, which encompass genetic, autoimmune, and post-inflammatory backgrounds, as well as origins that remain yet to be elucidated.

The planned research project will focus on identifying mutations in novel genes within a cohort of Polish patients with an initial clinical suspicion of (unspecified) phakomatosis, in whom previous analyses—including aCGH and a gene panel encoding proteins of the RAS-MAPK pathway—failed to verify the clinical suspicion of the disease. Although the research

project is only in its initial stages, it is already worth presenting the medical history of the first patient enrolled in the study cohort. The patient is a 4-year-old boy whose clinical presentation features phenotypic traits such as: pigmentation disorders, including CALMs (café-au-lait macules), a visual impairment, ligamentous and joint laxity, signs of motor clumsiness, sensory integration disorder, ADHD, and bilateral clinodactyly of the fifth finger. WES analysis was performed and revealed a variant of uncertain significance (VUS), c.6070T>C, in the *CSPG4* gene. According to current medical literature data, germline mutations in this gene might be a high risk to cause an NF1-like phenotype. WES analysis for the boy's parents is planned, and the results are likely to be obtained prior to the EuroDysmorpho 2026.

14:20, DECIPHERING THE MOLECULAR AND CLINICAL SPECTRUM OF RATARS

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Radio-Tartaglia syndrome (RATARS; OMIM #619312) is a neurodevelopmental disorder caused by *SPEN* (OMIM *613484) haploinsufficiency and characterized by global developmental delay/intellectual disability, behavioral abnormalities, distinctive craniofacial dysmorphisms, precocious puberty, and obesity, particularly in females. The syndrome was first described in 2021 based on clinical and molecular data from 34 individuals carrying truncating variants in *SPEN*. RATARS shares several clinical features with proximal 1p36 deletion syndrome, and affected females exhibit a distinctive X-chromosome DNA methylation (DNAm) signature.

Since the initial report, we have assembled a second large cohort comprising more than 50 affected individuals to further expand the phenotypic spectrum and better delineate the natural history of the disorder.

The clinical profile of this disease invariably includes developmental delay evolving in intellectual disability in the majority of individuals. Behavioral and psychiatric manifestations, including autistic features, anxiety, aggressive behavior, and attention-deficit disorder, were present in 81% of individuals. These features appear to evolve over time, with onset or worsening during puberty and a generally more severe presentation in females. Additional recurrent features included hypotonia (73%), brain and spinal anomalies (64%), congenital heart defects (28%), high or narrow palate (56%), brachydactyly (32%), precocious puberty (68% of females), and obesity or increased BMI, especially among females. Characteristic craniofacial features included broad forehead, frontal bossing, bitemporal narrowing, elongated arched eyebrows, synophrys, telecanthus, epicanthal folds, dysplastic ears, and a broad nose with a bulbous/prominent nasal tip worsening over time. Notably, treatment aimed at delaying precocious puberty appeared to improve behavioral and psychiatric manifestations in affected females.

DNA methylation studies are ongoing to further refine the X-chromosome episignature identified in affected females and to investigate the presence of an autosomal episignature for comparison with the episignature recently reported in 1p36 deletion syndrome.

In conclusion, the growing number of identified individuals suggests that RATARS is currently underdiagnosed. Our findings expand both the clinical and molecular spectrum of the disorder and provide important insights into its natural history, including sex-specific manifestations. These results are expected to improve clinical recognition, genetic counseling, and patient management.

14:30, DE NOVO ZNRF3 VARIANT IN A CHILD WITH PROGRESSIVE MACROCEPHALY AND PERIVENTRICULAR NODULAR HETEROTOPIA: EXPANDIND THE NEURORADIOLOGICAL SPECTRUM

Authors: Alessandra Spano1, Brach Del Prever Giulia2, Elisa Biamino3, Marco Spada1.

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Background: ZNRF3 encodes a transmembrane E3 ubiquitin ligase that downregulates canonical Wnt/β-catenin signaling. De novo missense variants clustering in the RING ligase domain were recently linked to a macrocephalic neurodevelopmental disorder (NDD) [Boonsawat et al AM J Human Genetics, 2024]. We report an anonymized child with marked macrocephaly and periventricular nodular heterotopia (PVNH) carrying a de novo ZNRF3 variant, suggesting expansion of the neuroradiological phenotype.

Methods: We reviewed longitudinal auxology and neurodevelopmental evaluations, EEG and serial brain MRI. First-tier genetics included array-CGH and PTEN testing; trio whole-exome sequencing (WES) was performed with phenotype-driven filtering and parental segregation.

Results: The girl was born at term with prenatal-onset macrocephaly (head circumference 39.5 cm,+2.2 SD), progressing to 60 cm (+6.7 SD) in early childhood. Height tracked ~50th centile; early-onset overweight with central adiposity was present. Motor milestones were mildly delayed (independent walking at 15 months) and expressive language delay required regular speech therapy and school support. Metabolic screening was unremarkable, and abdominal ultrasound and echocardiography were normal; physical exam showed no organomegaly or coarse features. MRI showed bilateral PVNH, regressing germinolytic cysts along the thalamo-caudate grooves, mildly dysmorphic lateral ventricles and mega cisterna magna. EEG showed sleep-activated anterior paroxysms. Trio WES identified a heterozygous de novo ZNRF3 c.991C>T (p.Pro331Ser) variant, likely pathogenic.

Conclusion: PVNH was not reported in the initial ZNRF3 macrocephalic NDD cohort. Our case indicates that neuronal migration defects may broaden the ZNRF3 spectrum and supports including ZNRF3 in the work-up of pediatric macrocephaly with PVNH and developmental delay.

14:40, UNUSUAL PRESENTATION OF SOTOS SYNDROME WITH SPONTANEOUS PNEUMOTHORAX IN A 16-YEAR-OLD MALE

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Sotos syndrome is a well-known monogenic syndrome, usually characterized by the triad of overgrowth, dysmorphisms and learning disability and caused by pathogenic variants in the *NSD1* gene. The cognitive profile is variable, with intellectual disability being absent from a minority of patients. Tall stature with long arms and possible joint laxity can put the syndrome into differential diagnosis with Marfan syndrome, although spontaneous pneumothorax is not usually associated with Sotos syndrome, with only three cases of this association reported in the literature to our knowledge.

We report the case of a 16-year-old male who came to our attention for spontaneous pneumothorax with a clinical suspicion of Marfan syndrome. Upon examination, the patient

presented with height exceeding the genetic target, macrocephaly and dysmorphisms including broad forehead with a high hairline, down-slanting palpebral fissures, synophria, hypertelorism and a long, narrow face with malar flattening, raising clinical suspicion of Sotos syndrome. There was no learning disability, aside from a reported slight dyscalculia. Exome sequencing was performed, prioritizing the analysis of in-silico panels of genes associated with overgrowth syndromes and collagenopathies. The analysis found the variant c.3230C>A p.(Ser1077Ter) of the *NSD1* gene, confirming the diagnosis of Sotos syndrome.

We here present a case with the very rare association of Sotos syndrome and spontaneous pneumothorax. Given the absence of intellectual disability, it is possible that the condition would have gone undiagnosed if not for the pulmonary presentation. Our case reinforces the association of spontaneous pneumothorax with Sotos syndrome and exemplifies the importance of detailed examination of dysmorphisms to guide genetic analysis.

14:50, WHEN IMPRINTING GOES VASCULAR: MOYAMOYA ANGIOPATHY IN SILVER-RUSSELL SYNDROME

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Moyamoya angiopathy (MMA) is a chronic cerebrovascular disorder characterized by progressive bilateral steno-occlusion of the supraclinoid internal carotid artery (ICA) and its main branches, and the development of a collateral network of fragile vessels ('moyamoya' in Japanese) in the deep areas of the brain. It could be an isolated and idiopathic finding, a consequence of environmental factors (i.e. head and neck radiotherapy), or it can be associated with genetic conditions (i.e. Trisomy 21, NF1, Noonan Syndrome).
We report a child presenting with poor growth, relative macrocephaly, characteristic facial features, soft palate cleft, hearing loss, and acute onset of TIA episodes, in whom neuroimaging revealed bilateral stenosis and near-occlusion of the ICAs with involvement of the ophthalmic/supraclinoid segments and marked reduction in arterial caliber, associated with extensive collateral circulation, consistent with a moyamoya-type angiopathy.
Given the peculiar overall picture, a WES analysis was performed within the Telethon Undiagnosed Disease Program (TUDP), revealing a de novo heterozygous variant in IGF2 gene: NM_000612.6:c.211T>C p.(Cys71Arg). The variant is classifiable as likely pathogenic according to ACMG guidelines, and its finding is consistent with a Silver-Russel type 3 diagnosis.

Silver-Russell (SRS)syndrome is a heterogeneous imprinting disorder characterized by prenatal and postnatal growth restriction, relative macrocephaly, facial dysmorphisms, and frequent body asymmetry, most commonly caused by 11p15 imprinting disturbances or maternal uniparental disomy of chromosome 7, with rare cases resulting from pathogenic variants in growth-regulating genes including IGF2.
While cerebrovascular anomalies are well recognized in Beckwith-Wiedemann syndrome, the epigenetic and phenotypic mirror disorder of SRS, they are only rarely reported in SRS, and moyamoya disease has not previously been described in association with SRS.
This discrepancy may reflect fundamental differences in growth factor signaling and epigenetic regulation between overgrowth and growth restriction states. IGF2 plays a central role in embryonic vasculogenesis, endothelial proliferation, and vascular smooth muscle maturation, and its disruption may impair vascular development and collateral vessel formation.
In addition, imbalance of the 11p15 imprinting network involving IGF2 and H19 may alter endothelial regulatory programs, including pathways related to angiogenic signaling, TGF-β modulation, and vascular stability. Epigenetically mediated effects on VEGF-dependent endothelial growth, as well as perturbations in NOTCH-driven arterial specification and vascular remodeling, may further contribute to abnormal cerebrovascular architecture.
Taken together, these mechanisms suggest that vascular anomalies in SRS may be underrecognized, and that IGF2-related disease may represent a biologically distinct subgroup with increased susceptibility to cerebrovascular involvement. This case expands the phenotypic spectrum of SRS and supports a mechanistic link between imprinting-dependent growth regulation and vascular development, raising the possibility that cerebrovascular anomalies such as moyamoya disease may be part of the broader, but incompletely defined, vascular phenotype of growth imprinting disorders.

15:00, UNMASKING HNRNPD-RELATED NEURODEVELOPMENTAL DISORDER: PHENOTYPIC EXPANSION AND INCIDENTAL DETECTION OF PARENTAL MOSAICISM

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Background: Heterogeneous nuclear ribonucleoproteins (hnRNPs) are RNA-binding proteins critical for RNA processing, with emerging evidence supporting their role in neurodevelopmental disorders (NDDs). Among these, *HNRNPD* has recently been proposed as a candidate NDD-associated gene implicated in neurodevelopmental impairment and characteristic dysmorphic features. To date, less than 15 individuals harboring intragenic pathogenic variants in the *HNRNPD* gene have been reported, suggesting Loss-of-Function

(LoF) with haploinsufficiency as the underlying disease mechanism. The full phenotypic and molecular spectrum remains poorly defined.

Case report: We report a 4-year-old child born to healthy non-consanguineous parents, presenting with severe speech delay, low-average cognitive functioning (IQ 86) with marked verbal/non-verbal discrepancy, delayed sphincter control, microcephaly and persistent sialorrhea. Dysmorphic features included brachycephaly, broad forehead, thin horizonta eyebrows, synophrys, hypotelorism, short smooth philtrum, thin upper vermilion border and large, anteverted, simplified ears. Brain MRI showed microcephaly with minor additional findings: inferior vermian hypoplasia, a small posterior fossa arachnoid cyst and mild peritrigonal white matter signal abnormalities.

Genetic testing: Trio-based SNP-array analysis and *FMR1* testing were unremarkable. Subsequent trio-based whole exome sequencing identified the novel heterozygous variant c.116_131delCGGCGGCGGGAAGCGG (p.Ala39Glufs58) in *HNRNPD* gene (NM_031370.3). This variant is predicted to introduce a premature stop codon, supporting a LoF effect, currently classified as likely pathogenic according to ACMG criteria. Segregation analysis demonstrated maternal mosaicism for the same variant.

Conclusion: We report a novel likely pathogenic loss-of-function variant in the *HNRNPD* gene associated with a neurodevelopmental disorder and distinctive dysmorphic features. This case expands the phenotypic and molecular spectrum of *HNRNPD*-related NDD and reinforces haploinsufficiency as the disease mechanism. The incidental identification of asymptomatic maternal mosaicism highlights the critical role of trio-based sequencing in accurate recurrence risk assessment and genetic counseling for rare NDDs.

Key words: *HNRNPD*, neurodevelopmental disorder, parental mosaicism

15:10, WDR44-RELATED CILIOPATHY WITH RENAL TUBULOPATHY AND HEPATOBILIARY INVOLVEMENT: A NOVEL DE NOVO VARIANT AND PHENOTYPIC EXPANSION

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Introduction

WDR44-related ciliopathy is an emerging X-linked neurodevelopmental disorder caused by variants in the WD40-repeat domain of *WDR44*, a negative regulator of ciliogenesis initiation acting through RAB11-dependent vesicular trafficking. To date, only twelve patients have been reported in the literature, with gain-of-function missense and nonsense variants as the predominant disease mechanism, and a single case attributable to a loss-of-function promoter deletion. The phenotypic spectrum encompasses developmental delay/intellectual disability, hypotonia, craniofacial dysmorphism, musculoskeletal abnormalities, and variable renal, cardiac, and brain involvement.

Case Report

We report a 15-year-old male, the thirteenth patient described worldwide with a molecularly confirmed *WDR44*-related ciliopathy. The proband presented at birth with microcephaly, neonatal hypotonia, and intrauterine growth restriction (birth weight 2400 g at term), with markedly increased nuchal translucency on first-trimester ultrasound. Chorionic villus sampling and subsequent array CGH were unremarkable. The neonatal course was complicated by acute cholestatic jaundice with paucity of bile ducts, spontaneously resolved; hepatic ultrasound demonstrated findings consistent with biliary hepatic fibrosis. Over time, the clinical picture evolved to include congenital renal tubulopathy with metabolic acidosis and chronic kidney disease (CKD stage II), ligamentous laxity with bilateral pes varus requiring surgical correction, recurrent otitis media managed with tympanostomy tubes, hypermetropia with esotropia, bilateral cryptorchidism requiring orchidopexy, and palatal crowding requiring orthodontic intervention. Cardiac evaluation was normal. Brain MRI performed at approximately 3–4 years of age was reported as normal. Neurodevelopmental assessment revealed global developmental delay with delayed ambulation (after age 2 years) and language delay; the most recent cognitive evaluation (WISC, 2023) yielded a full-scale IQ of 87, with relatively preserved verbal comprehension and reduced processing speed. On physical examination, notable dysmorphic features included epicanthus with hypotelorism, metopic ridge with biparietal narrowing, pterygium colli, anteverted nares, brachydactyly with tapering of distal phalanges, hockey-stick palmar crease, arched eyebrows, upslanting palpebral fissures, and a receding occiput.

Extensive prior genetic workup, including chromosomal microarray, targeted NGS panel for nephronophthisis, and whole-exome sequencing in trio (2021), had been unremarkable. Re-analysis of stored BAM files in 2025, performed with updated bioinformatic pipelines, identified a hemizygous de novo missense variant in *WDR44* [NM_019045.5: c.1994G>A, p.(Ser665Asn)], absent from gnomAD in hemizygous state, affecting a highly conserved

residue within the WD40-repeat domain, where all currently reported pathogenic gain-of-function variants cluster.

Conclusions

This case expands the phenotypic and mutational spectrum of *WDR44*-related ciliopathy, representing the thirteenth reported patient and the first with a prominent hepatobiliary involvement, including neonatal cholestasis with bile duct paucity and biliary hepatic fibrosis, broadening the known disease manifestations. Notably, the diagnosis was established only through reanalysis of existing sequencing data, underscoring the critical importance of periodic reinterpretation of non-diagnostic exome data in patients with unresolved complex phenotypes. Given the pleiotropic ciliopathy-related features of this disorder — including renal, hepatic, musculoskeletal, ophthalmological, and neurodevelopmental involvement — *WDR44* should be incorporated into next-generation sequencing panels designed for the diagnostic workup of ciliopathies and syndromic nephropathies in the pediatric setting.

15:20, ISOLATED COMPLEX CRANIOSYNOSTOSIS ASSOCIATED WITH A DE NOVO PATHOGENIC CHD8 VARIANT: INCIDENTAL FINDING OR EXPANSION OF THE PHENOTYPIC SPECTRUM OF CHD8-RELATED DISORDER?

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Craniosynostosis is a genetically heterogeneous condition characterized by premature cranial suture fusion, occurring in both isolated and syndromic forms. Established genetic causes include pathogenic variants in *FGFR1, FGFR2, FGFR3, TWIST1*, and *TCF12*, as well as chromosomal abnormalities such as 9p22–p24 deletions.

We report the case of a male 3-years-old child referred to our genetic outpatient clinic for isolated complex craniosynostosis. Chromosomal microarray analysis (CMA) did not identify

any pathogenic copy number variant. Trio whole-exome sequencing (WES) identified the pathogenic de novo variant *CHD8*: c.4384C>T – p.(Arg1462Ter). *CHD8* is a chromatin-remodeling gene associated with a neurodevelopmental disorder characterized by developmental delay, macrocephaly, autism spectrum features, and gastrointestinal manifestations (MIM #615032). Craniosynostosis is not a recognized feature of *CHD8*-related disorder. Therefore, the identified variant was initially considered an incidental finding, as the patient lacked the typical *CHD8*-related phenotype, showing age-appropriate neurodevelopment, normal growth parameters, and no macrocephaly. Sanger sequencing was performed using a different DNA sample and confirmed the presence of the *CHD8* de novo variant.

Craniosynostosis has been previously described in several chromatinopathies - including disorders caused by pathogenic variants in *KMT2D, KDM6A, KANSL1, KAT6B, and ASXL1* - suggesting that altered chromatin remodeling may contribute to abnormal cranial suture development through pleiotropic effect on gene regulation. In this context, this case report may expand the spectrum of phenotypes potentially associated with CHD8 pathogenic variants. We hypothesized that the lack of macrocephaly could be related to the presence of craniosynostosis. The absence of the neurodevelopmental impairment could be age-related, considering the very young age at diagnosis. Longitudinal neurodevelopmental follow-up was planned to determine whether additional CHD8-associated manifestations emerge with age. This case is presented with the additional aim of identifying further cases of CHD8-associated craniosynostosis through the present meeting.

15:30, EXPANDING THE MAB21L2 PHENOTYPE: A CASE WITH OCULAR ANOMALIES AND HIRSCHSPRUNG'S DISEASE

Authors: Gaia Visani[1], Silvia Kalantari[1,2], Marta Carboni[1], Simone Carbonera[1], Marta Melfa[1], Benedetta Inzoli[1], Maria Chiara Montalbano[1], Gabriela Anaya[1], Giovanna Riccipetitoni[3], Ilaria Palmieri[4], Enza Maria Valente[1,4], Fabio Sirchia[1,2]

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Both monoallelic and biallelic pathogenic variants of the *MAB21L2* gene have been reported in individuals with anophthalmia, microphthalmia and coloboma (AMC), with or without skeletal abnormalities. The phenotypic spectrum associated with the condition has yet to be

fully elucidated, exhibiting significant clinical variability that ranges from isolated AMC to more complex phenotypes.

We report the case of a 6-years-old male, presenting with Hirschsprung's disease and ocular abnormalities, such as bilateral lens opacity, microphthalmia, chorioretinal and optic nerve coloboma, and iris coloboma of the left eye. Besides the surgical treatment for Hirschsprung's disease, he had undergone surgical correction for an inguinal hernia and phimosis. Upon clinical examination, he presented with some facial dysmorphisms, i.e., high forehead, palpebral ptosis and epicanthus, wide nasal bridge and a high palate. He also exhibited narrow feet, with overlapping of the first and second toes of the left foot, and bilateral ungual dysplasia of the fifth toe.

Due to the clinical presentation, exome sequencing (ES) was performed, identifying a heterozygous variant of the gene *MAB21L2*: c.291C>A, p.(Cys97Ter). Parental segregation allowed us to confirm that the father also carried the same variant in a heterozygous state. No additional pathogenic or likely pathogenic variants associated with Hirschsprung's disease were identified through ES.

Upon more detailed examination, it emerged that the father was diagnosed with bilateral cataracts at the age of 30 and underwent surgical correction at 47. To further clarify his phenotype and highlight possible signs of *MAB21L2*-related manifestations, an ophthalmological evaluation was requested, which has yet to be performed. To date, the variants associated with the autosomal dominant form of the disease appear to be primarily missense. However, heterozygous loss-of-function variants have been reported in patients with ACM.

In conclusion, this case provides further delineation of the clinical spectrum associated with loss-of-function heterozygous variants of the gene *MAB21L2*, highlighting the variable expressivity even within family members. Moreover, this is to the best of our knowledge the first report of a patient with a *MAB21L2* variant in association with Hirschsprung's disease, suggesting a possible expansion of the phenotypic spectrum of the disease.

15:40, A COMPLEX PULMONARY PHENOTYPE IN A PATIENT WITH FGFR2-RELATED LADD SYNDROME

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LADD (Lacrimoauriculodentodigital) syndrome is a rare autosomal dominant congenital anomaly disorder caused by pathogenic variants in *FGFR2*, *FGFR3*, or *FGF10* genes. It primarily affects lacrimal and salivary ducts and glands, ears, teeth, and distal limbs, typically involving the thumbs. Additional manifestations may include facial dysmorphism, genitourinary abnormalities, and renal malformations. Pulmonary involvement has only rarely been described.

We report the case of a 20-year-old male with aplasia of the salivary and lacrimal glands, microtia with inner ear malformations, bilateral thumb agenesis, radial hypoplasia, and cystic hypodysplasia of the right kidney. The patient underwent several tests (prenatal karyotype, DEB test, and array-CGH) before receiving a diagnosis of LADD syndrome after identification of a heterozygous pathogenic *FGFR2* variant p.(Pro666Thr) through NGS sequencing at 9 years of age. He was subsequently referred to our center because of a complex interstitial lung disease presenting with recurrent spontaneous pneumothorax at 15 years of age. Chest imaging revealed diffuse bullous dystrophic changes, emphysema, bronchiectasis, and a reticular interstitial pattern. Cystic fibrosis, alpha-1 antitrypsin deficiency, hereditary connective tissue disorders, and Birt–Hogg–Dubé syndrome were all excluded through limited panel of genes prior to our consultation.

FGFR2 encodes a tyrosine kinase receptor involved in the TBX4–FGF10–FGFR2 signalling pathway, which regulates embryonic branching morphogenesis of several organs, including lungs, salivary and lacrimal glands, and limbs. Alterations of this pathway are associated with developmental abnormalities, including lethal pulmonary defects, mainly described in patients with *FGF10* variants. *FGFR2* variants described in LADD syndrome affect the tyrosine kinase activity of *FGFR2* probably leading to a reduced functional activity and generating developmental disturbances. However, pulmonary manifestations in patients with LADD syndrome are rarely reported.

Exome sequencing focused on monogenic pulmonary conditions was requested following our clinical genetics consultation in order to exclude other unidentified genetic causes potentially underlying the pulmonary phenotype. However, the central role of the TBX4–FGF10–FGFR2 pathway in embryonic development, raises the possibility that the rare pulmonary phenotype observed in our patient may represent an underrecognized manifestation within the phenotypic spectrum of *FGFR2*-related LADD syndrome.

Session 11 - Syndrome delineation

16:30, DIAGNOSTIC CHALLENGES IN CHROMOSOME 15Q11-Q13 IMPRINTING DISORDERS: THE PHENOTYPIC OVERLAPPING BETWEEN ANGELMAN SYNDROME AND PRADER-WILLI SYNDROME

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Background: Angelman syndrome (AS) and Prader-Willi syndrome (PWS) are distinct neurodevelopmental disorders caused by alterations in gene expression within the 15q11-q13 region. PWS results from the loss of paternally expressed genes, whereas AS is caused by the loss of maternally expressed genes, specifically impacting *UBE3A*. Despite distinct classic phenotypes, their clinical boundaries can blur due to shared genetic or epigenetic etiologies, leading to diagnostic dilemmas.

Case Presentation: We report a 15-year-old male with an ambiguous neurodevelopmental phenotype included severe intellectual disability, severe speech impairment (though not completely non-verbal), obesity with strong hyperphagia, impaired motor coordination with a wide-based gait, drooling, a happy disposition, sleep disturbances and behavioural issues, including self- and hetero-aggressive behaviours as well as skin picking. Prenatal ultrasound had detected fetal ventriculomegaly, but no genetic testing followed. Born at term via eutocic delivery, birth parameters were weight 3260 g (45th-50th), length 50 cm (50th), and head circumference 33 cm (10th-15th). Cryptorchidism was not reported. Parents reported a history of mild neonatal hypotonia, without sucking difficulties or failure to thrive. Current evaluation showed height 171 cm (50th), weight 81 kg (95^{th}), BMI 27.7 kg/m² (>97th), and head circumference 55 cm (35th-40th percentile), with mild nonspecific facial dysmorphism and mildly small hands. Seizures were absent. EEG and brain MRI were normal, except for left lateral ventricle posterior horn elongation and minimal periventricular white matter thinning. Prior Fragile X and array-CGH testing at another center were negative. Upon our initial evaluation, we performed clinical exome sequencing (CES) as the first-line test, which was non-informative. Subsequent Methylation-Specific Multiplex Ligation-dependent Probe Amplification (MS-MLPA) ruled out microdeletions/microduplications but revealed a loss of methylation within the 15q11.2 region. Finally, chromosome 15 microsatellite marker analysis excluded paternal uniparental disomy (UPD). Combined with MS-MLPA, this confirmed the

structural presence of a maternal chromosome 15 associated with an imprinting defect, establishing the diagnosis of Angelman syndrome.

Discussion: This case highlights the significant phenotypic overlap that can exist between AS and PWS, particularly when caused by imprinting center alterations. While large microdeletions typically yield classic presentations, imprinting defects—the rarest AS mechanism, accounting for only 3–5% of cases—can smooth out syndromic differences. This results in atypical, milder, or mixed phenotypes that lack textbook features, severely challenging clinical interpretation.

Conclusions: This case exemplifies the profound clinical complexity and phenotypic variability inherent to genetic syndromes, demonstrating how blurred or atypical presentations significantly contribute to diagnostic delay. It underscores that relying on textbook features is insufficient for complex 15q11-q13 neurodevelopmental disorders, making a comprehensive approach that integrates deep clinical characterization with precise molecular analysis paramount.

16:40, BEYOND FALSE LEADS: SMITH-MAGENIS SYNDROME UNMASKED BY REVERSE PHENOTYPING OVERRIDING A 22Q11.2 MICRODUPLICATION AND NON-DIAGNOSTIC SLC7A9 VARIANTS

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Introduction: In the era of advanced genetics, patients presenting with complex phenotypes may carry multiple genetic variants, some of which exhibit variable expressivity or are entirely incidental. Accepting these initial findings as a complete clinical explanation can create diagnostic blind spots, masking the true underlying aetiology.

Case Report: The female proband, fourth child of non-consanguineous parents, was born full-term via uncomplicated vaginal delivery. Neonatal admission was required due to a choking episode secondary to poor suction. Physical examination revealed craniofacial asymmetry,

low-set ears, almond-shaped eyes, rounded nose, retrognathia, high-arched palate, widely spaced nipples with an increased anteroposterior chest diameter, asymmetric Moro and marked axial hypotonia. Transfontanelar ultrasound identified peri/intraventricular haemorrhage (PVH/IVH) grade 3. During admission, metabolic testing was performed and showed hypercystinuria, raising suspicion for hypotonia-cystinuria syndrome. Sequencing of *SLC7A9* and *SLC3A1* identified three variants in *SLC7A9* (c.425T>C p.(Val142Ala), c.667C>A p.(Leu223Met), and c.505_508delCTGA p.(Ser169Cysfs*17)). Re-evaluation of these variants revealed that only one meets likely pathogenic criteria, with the remaining two being benign — excluding a recessive diagnosis of hypotonia-cystinuria syndrome, which had been prematurely assumed based on the initial biochemical and molecular findings. Given the proband's phenotype, chromosomal microarray was performed and identified a 22q11.2 microduplication, the same maternally inherited 2.18 Mb 22q11.2 microduplication previously identified in a half-sibling with learning difficulties. By age 14 months, at the medical genetics' appointment, the proband exhibited severe global developmental delay, profound generalized hypotonia (lacking head control at 10 months), right grade II vesicoureteral reflux, and unilateral sensorineural deafness. Neurosurgical assessment confirmed right unicoronal craniosynostosis causing the frontoorbital retrusion. Given a clinical presentation far too severe for the familial 22q11.2 microduplication, whole exome sequencing (WES) was performed, leading to the identification of a nonsense *de novo*, likely pathogenic, variant in *RAI1* (NM_030665.3:c.355C>T p.(Gln119*)), establishing a molecular diagnosis of Smith-Magenis syndrome (SMS), through a loss-of-function mechanism analogous to the more common 17p11.2 deletion.

Discussion: Reverse phenotyping validated the diagnosis, demonstrating that the patient's clinical features—specifically the retrognathia, almond-shaped eyes, low-set ears, rounded nose, chest dysmorphism, and severe neurological impairment— are consistent with an infantile presentation of Smith-Magenis syndrome. The marked craniofacial asymmetry was driven by the right unicoronal craniosynostosis, which may be related to one or both diagnosis (SMS or 22q11.2 microduplication). This case illustrates that one genetic finding does not preclude another. Premature diagnostic closure remains a critical pitfall in the era of broad genomic testing.

16:50, CLINICAL AND MOLECULAR CHARACTERIZATION OF KAUFMAN OCULOCEREBROFACIAL SYNDROME IN A TUNISIAN CHILD WITH A NOVEL UBE3B VARIANT

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Keywords : *UBE3B*, Kaufman oculocerebrofacial syndrome, Dysmorphism, Developmental delay

Kaufman Oculocerebrofacial Syndrome (KOS), also known as Blepharophimosis-Ptosis-Intellectual Disability Syndrome; BPIDS (MIM#244450) is a rare autosomal recessive disorder caused by pathogenic biallelic variants in *UBE3B* gene and characterized by developmental delay, intellectual disability, craniofacial dysmorphism, and multisystem anomalies.

We report a 4-year-old boy born to consanguineous parents, presenting with severe growth retardation, microcephaly (-3DS) and severe developmental delay with absence of speech and independent walking. Neurological manifestations also included febrile seizures, autistic features, swallowing difficulties with poor sucking and a history of transient congenital nystagmus.

Facial dysmorphism involved bitemporal narrowing, highly arched eyebrows, hypertelorism, downward slanting palpebral fissures, low-set protruding ears, broad nasal bridge, anteverted nares, long smooth philtrum, thin upper lip and micrognathia. Ectodermal anomalies showed sparse hair and adermatoglyphia. Additional features also included phimosis, syndactyly of the second and third toes, camptodactyly and hand contractures.

Ophthalmologic and audiometric examination respectively revealed reduced visual acuity associated to strabismus and unilateral mild hearing loss (30 dB threshold). Echocardiography, renal ultrasonography, and brain MRI and EEG were normal.

Whole Exome Sequencing identified a novel homozygous variant *UBE3B*: c.2705del (p.Gly902Aspfs*35), classified as likely pathogenic according to ACMG criteria (PVS1+ PM2_supporting), concordant with the diagnosis of KOS.

This case contributes to expanding phenotypic and mutational spectrum of *UBE3B*-related disease. Early molecular diagnosis is essential for patient management, prognosis assessment, and genetic counseling.

17:00, KCNK3-RELATED CHANNELOPATHY: A NEW DISORDER CHARACTERIZED BY DEVELOPMENTAL DELAY, DYSMORPHIC FEATURES AND ORGAN MALFORMATIONS

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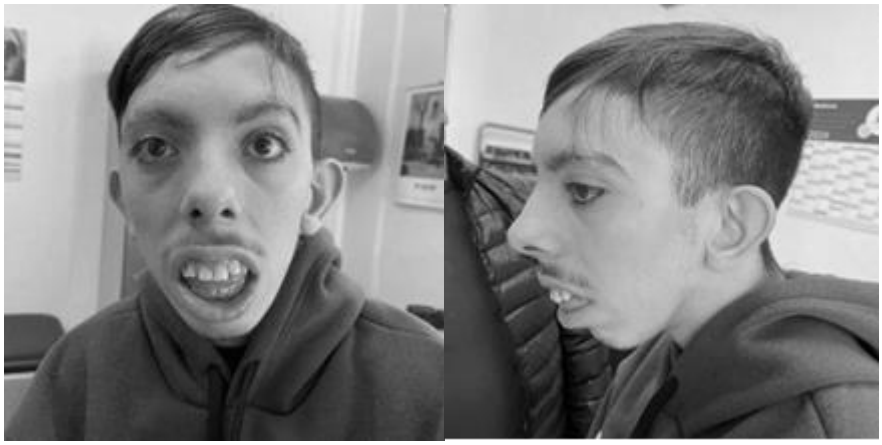
Introduction: KCNK3 gene encodes TASK-1, a pH-sensitive K+ channel expressed in neuronal cell populations and involved in the regulation of breathing. Heterozygous loss-of-function variants in KCNK3 gene are associated with pulmonary arterial hypertension, while gain-of-function variants have been recently described in 9 patients with hypotonia, global developmental delay, organ malformations and sleep apnea (Sörmann et al. 2022).
Case report: We describe the case of an 18-year-old boy with bilateral congenital clubfoot, cryptorchidism, developmental delay, severe intellectual disability and patent foramen ovale. The examination revealed short stature and low weight, relative macrocephaly (W: 1st ct; H: 3rd ct; OFC: 61st ct) and dysmorphic features: thick eyebrows, long eyelashes, hypertelorism, ectropion, broad nasal bridge, anteverted nostrils, retrognathia, high-arched palate, large and slightly cupped ears, bilateral palmar transverse folds, scoliosis, kyphosis and generalized hypertrichosis.
Material and methods: Karyotype analysis and array-CGH were performed with inconclusive results. NGS analysis through Clinical Exome Sequencing (CES) identified the heterozygous c.721C>T, p.(Leu241Phe) variant in KCNK3 gene, absent in GnomAD and classified as likely pathogenic (class 4, ACMG). The same variant has been previously identified in a 25-year-old woman with speech delay, hypotonia, obstructive sleep apnea and dysmorphic features (ptosis of the eyelids, elongated face).
Discussion: Here we describe the case of a young man affected by a new syndromic condition secondary to a heterozygous gain-of-function variant in KCNK3 gene and characterized by intellectual disability and distinctive dysmorphic features, recently described in a single study as a developmental disorder associated with sleep apnea. Variants occurring at the level of the fourth transmembrane helix (M4) seem to cause a milder phenotype with less severe cognitive impairment, no structural anomalies and only mild or absent sleep apneas. In agreement with the literature, our patient did not suffer from sleep apnea.



17:10, BILATERAL CHOANAL ATRESIA AND HEARING LOSS

M.A. is a 5-year-old female evaluated for clinical characterization regarding bilateral choanal atresia and hearing loss.

She is the second-born child; the family history is non-contributory. Born at term following an uneventful pregnancy, she presented at birth with bilateral choanal atresia, which was surgically corrected. Newborn hearing screening via otoacoustic emissions (OAEs) yielded a "refer" result bilaterally. Subsequent audiological evaluation revealed middle ear otodysplasia on the right side, for which hearing aid adaptation was indicated.

Motor development is age-appropriate. Conversely, difficulties in lexical and grammatical comprehension, as well as in phonological discrimination, have been reported, requiring educational support and speech therapy cycles.

Physical examination showed auxological parameters within normal limits (weight 19 kg at the 62th percentile, height 115 cm at the 97th percentile, head circumference 53 cm at the 97th percentile). No hypo- or hyperpigmented skin lesions were observed. Dysmorphic evaluation revealed a left preauricular fistula and a right branchial fistula, hypoplastic nipples, a broad forehead, thick eyebrows, dystopia canthorum, upslanting palpebral fissures, a long tubular nose with a high nasal bridge, a short philtrum, a thin upper lip, a high-arched palate, a crossbite, and microretrognathia.

Genetic analyses performed:

- **SNP array:** A ~300 Kb microduplication at the Xq21.1 locus, likely benign.
- **WES:** A heterozygous de novo variant, c.10744C>T (p.Arg3582Trp), in exon 38 of the KMT2D gene.

The presence of missense variants in a highly conserved region within exons 38 and 39 of the KMT2D gene has been recently associated with a new phenotype with

multiple malformations and absence of intellectual disability, registered in OMIM as branchial arch anomalies, choanal atresia, athelia, hearing loss, and hypothyroidism syndrome (BCAHH syndrome, OMIM# 620186). To date, fewer than 50 patients have been reported.

The phenotype is distinct from Kabuki syndrome and overlaps with the CHARGE spectrum. Phenotypic variability is broad, ranging from mild clinical presentations to more complex phenotypes. Although a specific gestalt is lacking, it is possible to recognize certain shared facial features among the reported patients, such as a broad forehead, long nose, short philtrum, and thin upper lip. Episignature analysis allows for the confirmation of borderline or ambiguous cases.

17:20, LATE DIAGNOSIS OF WIEDEMANN-STEINER SYNDROME IN AN ADULT: THE DIAGNOSTIC CHALLENGE

Authors (PHAN Ngoc Anh [1], LEHALLE Daphné[1])

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Background: Wiedemann–Steiner syndrome (WSS) is a rare chromatin-related neurodevelopmental disorder caused by pathogenic variants in KMT2A. Although the classical phenotype includes intellectual disability, short stature, hypertrichosis cubiti and distinctive facial features, adult presentations may be subtle and overlap with other chromatinopathies.

Case report: We report a 34-year-old woman, adopted from Vietnam in early childhood, referred for a first genetic evaluation because of mild intellectual disability. Perinatal history and biological family history were unavailable. No clear developmental delay was recorded. Schooling was marked by moderate learning difficulties, speech therapy, one repeated school year and later orientation to adapted education. She obtained a vocational diploma in laundry and currently works in a sheltered employment setting. She lives independently, manages daily activities and familiar transport, and is under reinforced curatorship mainly for administrative support.

Clinical examination showed a recognizable dysmorphic gestalt but was not typical of classical WSS. Facial features included narrow palpebral fissures, arched eyebrows, wide nasal bridge, anteverted nares, high-arched palate, and abnormal dentition. Importantly, the patient did not show the usual hair-related clues of WSS: hypertrichosis cubiti was absent, and there were no thick eyebrows, long eyelashes, or generalized hypertrichosis. We also noted mild short stature and distal limb anomalies, limb anomalies, including brachydactyly, particularly the fifth fingers, broad feet, and short toes. Because of the combination of mild intellectual disability, fifth-finger shortening, overlapping craniofacial presentation and lack of typical

hair-related WSS features, Coffin–Siris syndrome was initially considered. Solo genome sequencing identified a heterozygous splice-site variant in *KMT2A*, c.11322-1G>A, establishing the diagnosis of Wiedemann-Steiner syndrome.

Conclusion: This case illustrates that WSS may be underdiagnosed in adults, particularly when intellectual disability is mild, typical hypertrichosis is absent, and the phenotype overlaps with other chromatinopathies or syndromic neurodevelopmental disorders. Adult recognition of WSS should rely on the overall combination of craniofacial morphology, neurodevelopmental history, growth pattern, and associated multisystem features rather than on classical pediatric signs alone. Genomic testing is essential to establish the diagnosis and avoid persistent diagnostic uncertainty in mildly affected adults. Further adult-focused studies are needed to better define the natural history, comorbidities, and age-related evolution of WSS.

17:30, A CASE OF RNU4ATAC-OPATHY COMPLICATED BY CHILBLAIN-LIKE LESIONS AND SEVERE LUNG DISEASE ASSOCIATED WITH TYPE I INTERFERON PATHWAY DISREGULATION

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Background: Wiedemann–Steiner syndrome (WSS) is a rare chromatin-related neurodevelopmental disorder caused by pathogenic variants in KMT2A. Although the classical phenotype includes intellectual disability, short stature, hypertrichosis cubiti and distinctive facial features, adult presentations may be subtle and overlap with other chromatinopathies.

Case report: We report a 34-year-old woman, adopted from Vietnam in early childhood, referred for a first genetic evaluation because of mild intellectual disability. Perinatal history and biological family history were unavailable. No clear developmental delay was recorded. Schooling was marked by moderate learning difficulties, speech therapy, one repeated school year and later orientation to adapted education. She obtained a vocational diploma in laundry and currently works in a sheltered employment setting. She lives independently, manages daily activities and familiar transport, and is under reinforced curatorship mainly for administrative support.

Clinical examination showed a recognizable dysmorphic gestalt but was not typical of classical WSS. Facial features included narrow palpebral fissures, arched eyebrows, wide nasal bridge, anteverted nares, high-arched palate, and abnormal dentition. Importantly, the patient did not show the usual hair-related clues of WSS: hypertrichosis cubiti was absent, and there were no thick eyebrows, long eyelashes, or generalized hypertrichosis. We also noted mild short

stature and distal limb anomalies, limb anomalies, including brachydactyly, particularly the fifth fingers, broad feet, and short toes. Because of the combination of mild intellectual disability, fifth-finger shortening, overlapping craniofacial presentation and lack of typical hair-related WSS features, Coffin–Siris syndrome was initially considered. Solo genome sequencing identified a heterozygous splice-site variant in *KMT2A*, c.11322-1G>A, establishing the diagnosis of Wiedemann-Steiner syndrome.

Conclusion: This case illustrates that WSS may be underdiagnosed in adults, particularly when intellectual disability is mild, typical hypertrichosis is absent, and the phenotype overlaps with other chromatinopathies or syndromic neurodevelopmental disorders. Adult recognition of WSS should rely on the overall combination of craniofacial morphology, neurodevelopmental history, growth pattern, and associated multisystem features rather than on classical pediatric signs alone. Genomic testing is essential to establish the diagnosis and avoid persistent diagnostic uncertainty in mildly affected adults. Further adult-focused studies are needed to better define the natural history, comorbidities, and age-related evolution of WSS.

17:40, THE IMPORTANCE OF PARENTAL PHENOTYPING AND CLINICAL–LABORATORY INTEGRATION IN THE DIAGNOSIS OF AN FLNA-RELATED DISORDER: A CASE REPORT

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Background

The interpretation of genomic sequencing data requires close integration between clinical evaluation and collaboration with the genetics laboratory, particularly in conditions with variable expressivity. Phenotypic assessment of the parents may be crucial in guiding the diagnostic hypothesis and supporting the identification of potentially relevant inherited variants.

Case report

We report the case of an 11-year-5-month-old girl, the second child of non-consanguineous parents, with an apparently negative family history for genetic disorders. At birth, a complete left cleft lip and palate was identified and subsequently surgically repaired. The patient presented with global developmental delay, independent walking achieved at 2 years of age, language disorder with persistent phonetic-phonological errors, and specific learning

disorder. Neurological evaluation and EEG were unremarkable, while brain MRI revealed multiple periventricular nodular heterotopias. A patent ductus arteriosus (PDA) with low-velocity left-to-right shunt was also present, associated with easy fatigability during prolonged exertion. Laboratory investigations showed mild thrombocytopenia (platelet count 148×10^9/L).

Physical examination revealed minor craniofacial anomalies, narrow thorax with upper pectus carinatum and mild lower pectus excavatum, mild dorsal scoliosis, generalized joint hypermobility (Beighton score 8/9), soft doughy skin, arachnodactyly, and body disproportion with a relatively long trunk compared with the limbs. Maternal clinical evaluation also demonstrated joint hypermobility (Beighton score 5/9).

Array-CGH performed at approximately 1 month of age was normal. Trio whole genome sequencing (WGS) was proposed, after preliminary discussion with the laboratory regarding the clinical suspicion of an FLNA-related condition with possible maternal inheritance. Analysis identified the maternally inherited heterozygous FLNA c.2527del variant (p.Ala843Leufs*33), classified as likely pathogenic. FLNA-related conditions are X-linked dominant disorders characterized by marked phenotypic variability, including periventricular nodular heterotopia, congenital heart defects, vasculopathies and aortopathies, respiratory and gastrointestinal manifestations, ligamentous laxity, and macrothrombocytopenia. Such clinical variability may be influenced by skewed X-chromosome inactivation mechanisms.

Conclusions

This case highlights the value of extending clinical evaluation to family members in the interpretation of genomic data and in the diagnostic definition of conditions with variable expressivity, particularly when inherited from a parent. Close collaboration between clinicians and the genetics laboratory enabled WGS analysis to be directed toward an inherited variant consistent with the observed phenotype. Molecular diagnosis also allowed the implementation of targeted multisystem follow-up in both the proband and her mother, with particular attention to potential cardiovascular and respiratory complications associated with FLNA-related conditions.

17:50, MIGHT SOX4 BE AN OVERLOOKED SYNDROMIC MODY GENE?

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Background: Monoallelic *SOX4* variants have been associated with a rare autosomal dominant neurodevelopmental disorder (SOX4-ND, OMIM #618506), characterized by developmental delay, mild intellectual disability (ID), behavioral abnormalities, facial dysmorphisms and multisystem congenital anomalies. Less than 30 affected individuals have been reported to date in medical literature, and the clinical spectrum is therefore still poorly defined. MODY (maturity-onset diabetes of the young) is an early-onset diabetes with absence of autoantibodies, usually non-syndromic and inherited as an autosomal dominant trait.

Case report: A 14-year-old boy was referred to our Medical Genetics Unit for suspected monogenic diabetes and deafness following negative results on a MODY gene panel requested by his diabetologist.. A comprehensive clinical re-evaluation revealed a broader syndromic phenotype, including neurodevelopmental disorder, speech delay, learning difficulties and dysmorphic facial features. Array-CGH analysis was normal, while exome sequencing identified a *de novo* likely pathogenic variant in *SOX4* (c.377A>G; p.Tyr126Cys). Due to the potential new identified correlation, we presented our case to the working group of the Italian Society of Human Genetics (SIGU) to identify additional individuals with *SOX4* variants and unexplained diabetes. This collaborative effort led to the identification of two further unrelated individuals with SOX4-ND and adolescent-onset diabetes harboring distinct *de novo SOX4* variants – [p.(Phe66Leu) and p.(Lys118Asn)]. All reported *SOX4* variants affect conserved residues within the HMG-box DNA-binding domain. All three patients exhibited core features of SOX4-ND, including mild intellectual disability and facial dysmorphism. Targeted analysis of established MODY genes was performed in all cases and yielded negative results.

Conclusion: Members of the SOX family of transcription factors play pivotal roles in many developmental and pathological processes. Among them, *SOX4* is the most highly expressed in pancreatic islets and murine models confirm the involvement of *SOX4* in pancreatic development and insulin secretion. The association of *SOX4* variants and diabetes is thus biologically plausible, although has not been previously reported. Our findings suggest that MODY-like diabetes may represent an early-onset and potentially underrecognized feature of SOX4-ND, supporting the need for targeted metabolic surveillance in affected individuals.

Conversely, the syndromic manifestations of SOX4-ND can be subtle and easily overlooked, particularly when genetic tests is performed prior to clinical genetics evaluation. These observations support the inclusion of *SOX4* sequencing in MODY *in silico* gene panels.

18:00, WHEN A GENETIC DIAGNOSIS CHANGES OVER TIME: RE-EVALUATION OF AN FBN2 VARIANT PREVIOUSLY ASSOCIATED WITH BEALS SYNDROME

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Here we present the case of an adult woman referred to our Clinical Genetics Unit for reassessment of a long-standing diagnosis of congenital contractural arachnodactyly, also known as Beals syndrome, originally based on a familial FBN2 variant identified in 1997.

The historical molecular result, reported as T3799C in exon 29 of FBN2, had been considered diagnostic in the family. The same variant was also originally reported in the patient's son, who presented at birth with arthrogryposis involving the hands, elbows, hips and knees, and in a sister diagnosed with skeletal anomalies compatible with Beals syndrome. Other siblings had tested negative for the familial variant.

The patient came for a clinical geneticsAt re-evaluation after 29 years from initially diagnosis, the patient showed only mild and non-specific connective tissue-related findings, including kyphoscoliosis, bilateral fifth-finger camptodactyly, mild bilateral pes cavus, mild genu valgum and piezogenic papules. Thumb and wrist signs were negative, with no relevant joint hypermobility or major cardiovascular involvement documented.

Given the time elapsed since the original diagnosis and the evolution of variant interpretation criteria, targeted reassessment was performed. The variant was re-annotated as FBN2 NM_001999.4:c.3799A>G and confirmed in heterozygosity. However, according to current evidence, it is now classified as a variant of uncertain significance (ACMG criteria: PM2, PP3 supporting). Therefore, the previous molecular diagnosis of Beals syndrome cannot be considered genetically molecularly confirmed at present.

This case illustrates how genetic molecular diagnoses may change over time. Variants interpreted before the availability of modern population databases, standardized

classification frameworks and updated bioinformatic tools should be periodically re-evaluated, particularly when the phenotype is incomplete or only partially concordant.

In conclusion, we report a familial case in which a historical FBN2 based diagnosis was revised after contemporary variant reassessment. Periodic reinterpretation of genetic findings is essential for accurate diagnosis, clinical surveillance, recurrence risk assessment and genetic counselling. Further clinical and molecular re-evaluation of the affected son is has been planned in order indicated to clarify the familial phenotype.

Saturday 19 September

Session 12 Syndrome delineation

9:10, COPB1 GENE ASSOCIATED BARALLE-MACKEN SYNDROME – A RARE COATOPATHY. MORPHOLOGICAL OBSERVATIONS AND DIFFERENTIAL DIAGNOSTIC CONSIDERATIONS

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Background

Recently, biallelic variants in *COPB1* have been shown to cause a novel syndromic intellectual disability, the Baralle-Macken syndrome (MIM #619255) (PMID: 33632302). The clinical and immunological phenotype was further delineated by Khalid et al. (PMID: 40396222) and Alroqi et al. PMID: 40396222). Until now, only about ten individuals were described. *COPB1* encodes the coatomer subunit beta protein, which is essential for intracellular protein trafficking and as such, for brain development.

Case report

We present a male child of Hungarian Roma descent with Baralle-Macken syndrome with developmental delay, movement disorder, frequent respiratory tract infections and facial features that show substantial overlap with deletion 22q11.2 syndrome.

Materials and methods:

Array CGH was performed using Affymetrix CytoScan 750K and data were analysed by Chromosome Analysis Suite (ChAS) v2.0 Software (Affymetrix, Thermo Fisher Scientific).

Whole exome sequencing (WES) was performed using the Twist Exome 2.0 plus Comprehensive Exome Spike-in kit on a NextSeq 2000 sequencer (Illumina). Raw data was analysed using an in-house linux pipeline and the VarSeq Software (GoldenHelix). Variants were classified according to the ACMG guidelines.

Results

Multiple chromosomal ROH-es (regions of homozygosity) were detected using array CGH throughout the genome, although the parents had no knowledge on consanguinity. WES revealed a likely pathogenic variant within one of the ROH regions (11p15.4p13), in the *COPB1*

gene NC_000011.10(NM_001144061.2):c.957+1G>T, affecting a splice donor site. The variant was described in ClinVar (ID 996016) as pathogenic/likely pathogenic causal for Baralle-Macken syndrome, but was only desribed once in two females of Polish-Roma descent. It was functionally studied by Macken et al., 2021.

Discussion

Two previously reported individuals and our case harbour the same c.957+1G>T variant in the *COPB1* gene raising the possibility that this might actually be a founder variant occurring in the Roma population. We elaborate on the morphological features and based on our case, we warrant differential diagnosis from 22q11.2 deletion syndrome, considering overlap with disturbed T-cell immunity, neurodevelopmental nature and certain facial features.

9:10, LONG FOLLOW UP OF A GIRL WITH VISSERS-BODMER SYNDROME

Radka Kremlíková Pourová

We present a 12-y-o girl followed up at our Department since her 8th month. She was introduced with short stature, submucosal cleft palate, distingtive facial dysmorphy, failure to thrive and hearing loss.

During our monitoring she developer mild to moderate psychomotoric development delay, but the hearing loss was revoked after succesful cleft surgery. Nowadays she presents short stature (even after GH therapy), facial dysmorphy, intellectual diability and autistic features. At the age of 10 she was diagnosed with de novo *CNOT1* mutation.

9:20, DDX1 HAPLOINSUFFICIENCY DISRUPTS CELLULAR STRESS RESPONSES AND CAUSES A NEURODEVELOPMENTAL DISORDER

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Background:
RNA helicases are emerging as critical regulators of human neurodevelopment. Neurons are particularly vulnerable to stress-inducing agents, and emerging evidence indicates that disruption of cellular stress response pathways during early neurodevelopment can impair neuronal maturation and connectivity. DEAD/DExH-box RNA (DDX) helicases are key regulators of RNA metabolism and cellular stress responses, and their dysfunction has been

associated with distinct neurodevelopmental syndromes.

Materials and Methods:
We identified nine individuals from nine unrelated families harboring *de novo* variants in the DEAD-box RNA helicase gene *DDX1*, an essential regulator of cellular responses to genotoxic and environmental stress. All variants were ultra-rare, affected highly conserved residues within critical functional motifs, and were predicted to be deleterious by in silico analyses. Functional studies were performed using patient-derived fibroblasts to assess the mono-allelic effects of *DDX1* variants on cellular stress responses.

Results:
Affected individuals presented with a recognizable neurodevelopmental syndrome characterized by developmental delay, intellectual disability, hypotonia, behavioral dysregulation, and a distinctive facial gestalt associated with recurrent craniofacial and musculoskeletal abnormalities. Cells carrying pathogenic *DDX1* variants showed impaired radiation-induced DNA double-strand break repair, defective protection of specific target mRNAs under oxidative stress conditions, increased production of reactive oxygen species, and reduced mitochondrial function. These findings indicate that disease-associated *DDX1* variants disrupt multiple stress-related functions of the helicase.

Conclusion:
Our findings establish *DDX1* as a novel cause of neurodevelopmental disorder and indicate that DDX1 functional haploinsufficiency reduces the capacity of developing neurons to withstand stress-induced damage, thereby contributing to neurodevelopmental disruption in humans.

Keywords: DDX1; RNA helicase; cell stress response; DNA damage response; oxidative stress; neurodevelopmental disorders.

9:35, VARIABLE PHENOTYPE OF PATIENTS WITH WIEDEMANN-STEINER SYNDROME: CASE SERIES FROM THE SINGLE CENTER

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Background: Wiedemann-Steiner syndrome (WSS) is characterized by developmental delay, intellectual disability, and characteristic facial features, with or without additional congenital anomalies. Distinctive feature is hypertrichosis cubiti or other body parts. We report 4 cases of WSS with variable phenotype features.

Case 1: 5 years old girl at age of 2 years referred to clinical genetics due to developmental delay and failure to thrive. She also had small atrial septal defect. She is on follow up for the myopia. She had downslanted palpebral fissures, hypertelorism, long eyelashes, wide nasal bridge, broad nasal tip, thin vermilion of the upper lip, micrognathia and sacral dimple. Whole exome sequencing (WES) showed likely pathogenic frameshift variant in KMT2A gene NM_001197104.2(KMT2A):c.3922C>T, (p.Gln1308Ter).

Case 2: 16 years old girl at age of 15 years referred to clinical genetics for the mild intellectual disability, behavioral abnormalities, corpus callosum defect, short stature (GH deficiency), hypertrichosis, foot deformities and feeding difficulties in infancy. She presented with thick eyebrows downslanted palpebral fissures, epicanthus, foot II-III digits syndactyly, fifth finger clinodactyly. WES showed likely pathogenic nonsense variant in KMT2A gene NM_001197104.2(KMT2A):c.3614dup, (p.Tyr1205Ter).

Case 3: 13 years boy referred to clinical genetics for the mild intellectual disability, Klippel-Feil syndrome: C1 vertebral dysplasia and C2/C3 fusion. The patient was born prematurely at 29th week of gestation. He presented with downslanted palpebral fissures, hypertelorism, broad nasal tip, thin vermilion of the upper lip, hand deviation, IV and V finger clinodactyly, puffy hands and foot. WES showed de novo missense variant in KMT2A gene NM_001197104.2(KMT2A):c.4351T>C, (p.Cys1451Arg).

Case 4: 15 years old girl at age of 13 years referred to clinical genetics due to microphthalmia, strabismus, high grade myopia and hirsutism. She had normal development and normal school performance. She presented with downslanted palpebral fissures, hypertelorism, broad nasal tip, left ptosis. WES showed missense variant in KMT2A gene NM_001197104.2(KMT2A):c.6214T>C, (p.Cys2072Arg).

Discussion: 3/4 patients presented with intellectual disability and 1 patient was normal development as known from the literature that 3% are without intellectual disability. All patients presented with typical dysmorphism for WSS. 2/4 patients presented with hypertrichosis. Additional congenital anomalies included atrial septal defect, vertebral anomalies and ophthalmic issues (strabismus, myopia, ptosis) with endocrine pathology. Missense variants can be related with atypical presentation of WSS.

Conclusion: WSS can present with various clinical features, but distinctive facial features are cardinal. Even patients with normal developmental should be considered to have WSS.

9:50, GENETIC MOSAICISM – DIAGNOSES WE ALMOST MISSED

Manuel Michels[1], Svenja Daschkey[1], Jutta Dietzel-Dahmen[1], Matthias Drechsler[1], Monica Naujoks[2], Alena Welters[3,4], Beate Betz[1], Cornelia Blank[1], Walburga Vorhoff [5], Teresa Neuhann 6, Lisa Senninger 6, Jörg Schaper[3], Sugirthan Sivalingam[1], Silke Redler[1], Fei Song[1], Dagmar Wieczorek [1,3]

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For decades, human genetics focused mainly on germline mutations. Current evidence indicates that genetic mosaicism plays an important role in the pathogenesis of rare diseases, including neurodevelopmental disorders and skeletal anomalies. Even with state-of-the-art sequencing platforms, low-level or tissue-restricted mosaic variants frequently escape detection, either because their allele fractions fall below analytical thresholds or because they are confined to specific cell types. Affected individuals with mosaicism can produce misleading atypical or mild clinical signs.

We report on three affected individuals with low-grade mosaicism and will demonstrate the pitfalls in establishing the correct diagnosis.

Individual 1 is a 13-year-old boy with intellectual disability, significant body asymmetry, and skin and hair pigmentation anomalies. At birth, feeding difficulties and muscular hypotonia were noted. cMRI revealed microcephaly without brain malformations. A 20% mosaic terminal deletion 5p13 with a size of 37 Mb in fibroblasts was identified, establishing the diagnosis of cri du chat syndrome without the typical clinical manifestations (Daschkey *et al.*, 2026).

Individual 2 is a 12-year-old girl with tall stature, dysmorphic features, developmental delay, and congenital anomalies. A likely pathogenic mosaic *EED* variant was identified with a 31% variant allele fraction in peripheral blood using exome sequencing. Mosaicism was also detected in buccal mucosa (11% and 17%) and saliva (30%) by deep sequencing, indicating somatic mosaicism in multiple tissues. DNA methylation profiling revealed a high-confidence epigenetic signature consistent with a *PRC2* complex-associated disorder, further supporting the pathogenicity of the identified variant (Song, Michels et al, manuscript in revision).

Individual 3 is a 6.5-year-old girl (one triplet sister and one triplet brother) with multiple enchondromatoses and multiple exostoses involving different bones, e.g. phalanges, forearm, tibia and calcaneus. Panel and exome analyses did not reveal a pathogenic variant. Radiologically the diagnosis of metachondromatosis was established and whole genome sequencing was performed. This helped to identify a deep intronic *de novo* likely pathogenic variant in *PTPN11*, which showed a low-grade mosaicism of 11%.

These cases underscore that low-grade mosaicism should be a key consideration in patients who remain undiagnosed after exome or genome sequencing, particularly when asymmetry, pigmentary anomalies, or other mosaicism-suggestive signs are present. Accurate detection demands sufficient sequencing depth, interrogation of multiple tissue sources, and meticulous phenotypic documentation. By integrating these strategies, clinicians can uncover cryptic mosaic variants and achieve definitive molecular diagnoses.

10:05, KDM5B-RELATED NEURODEVELOPMENTAL DISORDER: VARIABLE EXPRESSIVITY AND SUBTLE DYSMORPHISM IN FOUR PATIENTS WITH NOVEL HETEROZYGOUS VARIANTS

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Introduction: *KDM5B* encodes a histone H3K4 demethylase involved in chromatin regulation and neurodevelopment. While biallelic disruptive variants cause intellectual developmental disorder 65 (MIM #618109), recent evidence supports an emerging dominant KDM5B-related neurodevelopmental disorder associated with developmental delay/intellectual disability (DD/ID), speech impairment, autistic features and variable dysmorphism. However, interpretation of heterozygous variants remains challenging because of reduced penetrance and marked phenotypic variability.

Case Series: We report four unrelated patients with syndromic neurodevelopmental disorder carrying previously unreported heterozygous *KDM5B* variants identified by trio whole-exome sequencing. Two patients harbored likely pathogenic loss-of-function variants: c.2671C>T, p.(Gln891Ter), inherited from a mildly affected mother, and *de novo* c.4022-1G>C. Two carried missense variants of uncertain significance: *de novo* c.4484C>G, p.(Pro1495Arg), and paternally inherited c.126C>G, p.(Phe42Leu), with learning difficulties in the transmitting father.

All patients presented with developmental delay, with prominent speech and language involvement ranging from articulatory disorder to severe expressive language delay with regression and autistic features. Cognitive impairment ranged from borderline intellectual functioning to moderate intellectual disability. Macrocephaly or relative macrocephaly was present in three patients. Dysmorphic features were mild and variable, including broad forehead, abnormal ears, micro/retrognathia, flat nasal bridge or mild midface hypoplasia, and upper vermilion abnormalities, without a distinctive facial gestalt. Additional findings included unilateral renal agenesis, growth hormone deficiency, joint hypermobility, unilateral cryptorchidism and dental malocclusion. None had epilepsy.

Conclusions: Our observations further support the emerging dominant KDM5B-related phenotype and highlight the combination of language-predominant neurodevelopmental impairment, macrocephaly or relative macrocephaly, and subtle craniofacial anomalies as a potentially useful clinical clue. The presence of mildly affected transmitting parents reinforces the role of reduced penetrance and variable expressivity in KDM5B-related disorder, emphasizing the importance of detailed parental phenotyping and segregation analysis for variant interpretation and genetic counselling.

10:20, CLINICAL AND MUTATIONAL SPECTRUM OF SEC23A-RELATED DOMINANT CRANIO-LENTICULO-SUTURAL DYSPLASIA

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Keywords: Cranio-lenticulo-sutural dysplasia, SEC23A, genotype-phenotype correlation

Background: Cranio-lenticulo-sutural dysplasia (CLSD, OMIM #607812) is characterized by craniofacial anomalies, short stature, and frequent ocular involvement. It is caused by recessive or dominant variants in SEC23A, with the dominant form reported in only a limited number of patients. This study aims to expand current knowledge of CLSD by refining its clinical spectrum and natural history, comparing dominant and recessive forms, and exploring genotype–phenotype correlations to address future pathogenic studies.

Materials and Methods: Through an ERN-ITHACA (#311) call for collaboration, we collected six individuals with CLSD, all diagnosed by whole-exome or whole-genome sequencing.

Results: We studied three affected individuals in one family (a 6-year-old boy, his 6-month-old sister, and their father) (Fig.1-2) as well as three sporadic patients (a 14-year-old boy, 10-year-old boy and a 2-year-old boy). All showed large fontanels, delayed cranial ossification with wide sutures (Fig.2), frontal bossing, hypertelorism, a thin prominent nose, down-slanting palpebral fissures, high-arched palate and mild developmental delay. A heterozygous SEC23A variant c.1795G>A (p.Glu599Lys) was identified in the familial cases, a heterozygous de novo variant c.1796A>G (p.Glu599Gly) was detected in patient 4, while the same heterozygous variant c.2146C>T (p.Arg716Cys) was identified as de novo in patients 5 and 6.

Conclusion: The ERN-ITHACA collaboration remains open to recruit additional patients. The absence of ocular involvement distinguishes our dominant CLSD cases from previously reported recessive forms. Larger cohorts are needed to refine clinical variability, strengthen genotype–phenotype correlations, and support molecular studies (like RNAseq analysis) to further investigate the effect and the role of SEC23A variants in CLSD.

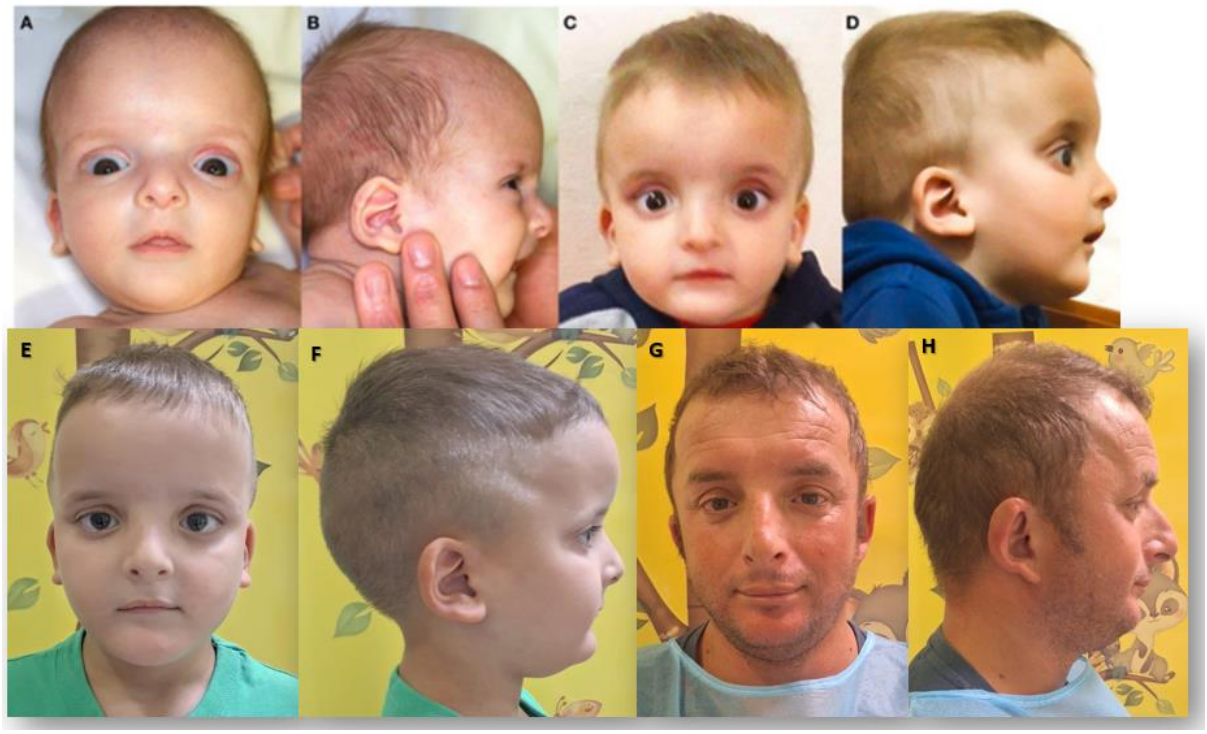

FIGURE 1 (a–h) Facial phenotype of patient 1 at age 2 month (a,b) at age 18 months (c,d) and at age 5 years (e,f). Note large forehead, hypertelorism, downslanting palpebral fissures and thin nose with hypoplastic alae nasi. There is a striking resemblance to the individuals reported by Boyadjiev et al. (2003, 2006, 2011). Panel (g, h) shows the patient's father (patient 3) as an adult. His facial features include the large forehead, hypertelorism and thin nose.

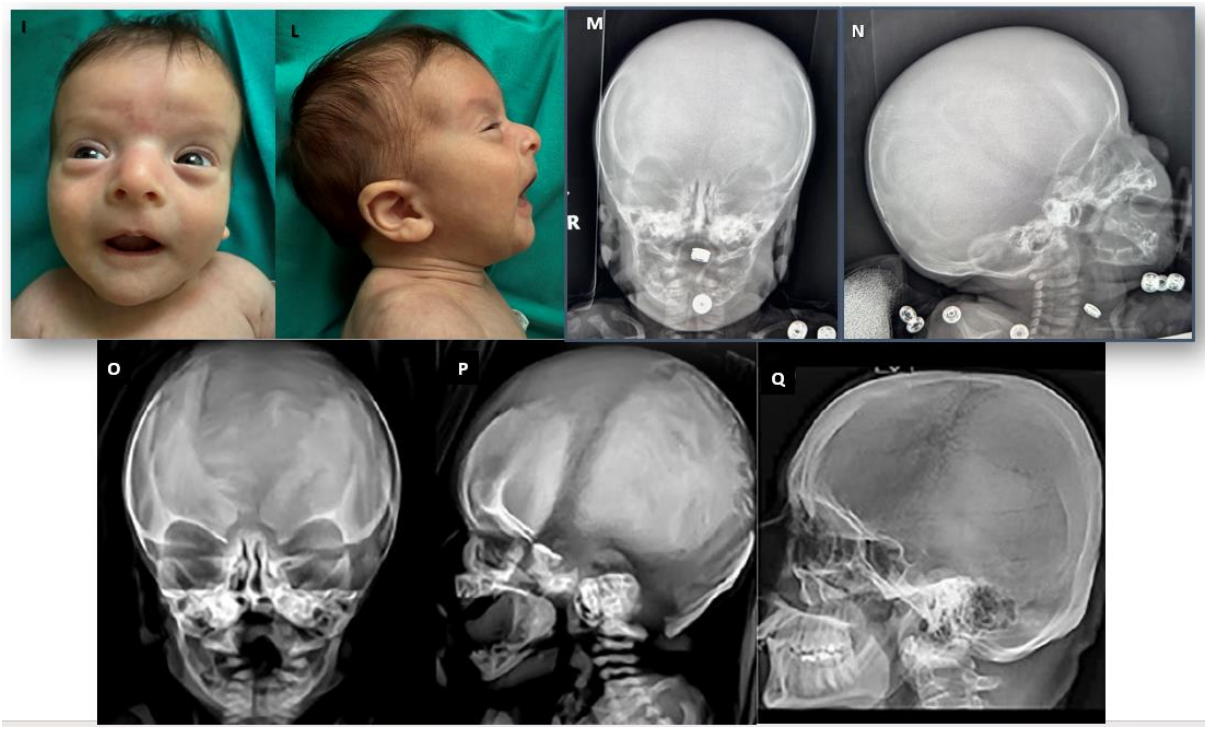

FIGURE 2 (i-q) Facial phenotype of patient 2 (sister of patient 1) at age 4 months (i,l). Note large forehead, hypertelorism and thin nose Panel shows the skull radiographs of patient 2 (m,n) and patient 1 (o,p) at birth, with very incomplete ossification of the frontal, parietal, and occipital bones leaving large sagittal and coronal sutures (lambdoid suture not well visible). In the lateral skull radiograph of the father (patient 3) (panel q), the fontanels are close but the frontal sinuses have failed to develop.

Session 13 Syndrome delineation

10.35, CLINICAL AND GENOMIC ENDOPHENOTYPES OF PITT-HOPKINS SYNDROME

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BACKGROUND. Pitt–Hopkins syndrome (PTHS) is a neurodevelopmental disorder characterized by a distinctive clinical phenotype that includes severe intellectual disability (ID), absent speech, breathing anomalies, and typical facial features, caused by *TCF4* haploinsufficiency. Genetic and clinical heterogeneity in PTHS is an emerging issue.

METHODS. We performed a comparative evaluation of 60 individuals carrying *de novo* pathogenic variants in *TCF4*. In addition to chromosomal microarray analysis (CMA), multiplex ligation-dependent probe amplification (MLPA), and exome sequencing (ES), properly applied to all patients, genetic analyses included standard karyotyping, optical genome mapping (OGM), and cDNA studies in selected cases. Individual clinical phenotypes were assessed through direct physical examinations and standardized developmental scale evaluations, by questionnaires aimed at defining a "neuroclinical score."

RESULTS. We identified three main clinical–genomic categories in the field of PTHS: 1) A total of 45 patients (75%) presented with the full and severe PTHS phenotype, according to the

consensus clinical score. These case were associated with loss-of-function (LoF) variants in exons 9 –18 (42/45), *de novo* balanced translocations affecting *TCF4* detected by conventional karyotyping (2/45), and one 2 Mb inversion disrupting *TCF4* detected by OGM; 2) two patients (3%) with LoF variants in exons 7 and 8 showed fluent speech and a shared facial and neurodevelopmental phenotype distinct from typical PTHS, confirming the data already reported in the literature; 3) the remaining 13 patients (22%) displayed highly variable clinical presentations, that was very mild in some cases, associated with missense or synonymous variants affecting exons 12–18 (*Figure 1*).

Two additional patients harboring partial *TCF4* deletions (not extending beyond exon 5) were misdiagnosed with PTHS despite exhibiting only borderline intellectual disability. Accordingly, these patients are not included in the patient series discussed here (*Figure 2*).

From a neuropsychological point of view, variables showing the most significant differences among the three groups were: ID (Non-verbal scales), gross motor skills, sleep (SDSC Scale), behaviour (ADI-R Scale) and communication (CFCS).

CONCLUSIONS. Thanks to the simultaneous and longitudinal analysis of a large series of patients, we were able to get new insights in the field of PTHS. Clinical and genomic data are presented with the aim of: 1) providing tools for individual prognostic assessment; as suggested for the first time a “neuroclinical score” assessing the most relevant neurological features can help; 2) sharing with the scientific community the critically relevant features for the precision diagnosis of a very rare condition such as PTHS; 3) characterizing the individual neurodevelopmental phenotype as a starting point to evaluate the efficacy of any novel therapeutics.

Figure 1: Main clinical–genomic categories: a) full phenotype with LoF variants (frameshift, nonsense) in exons 9-18; b) milder phenotype with LoF variants (frameshift, nonsense) in exons 7-8; c) and d) variable but milder phenotype with missense or hypomorphic variants exons 9-18: Figure 1c: missense variant exon 18; figure 1d: c.990G>A (p.Ser330=) in exon 12.

- Fluent speech (IQ 76)
- No respiratory abnormalities
- No ataxic features
- Mild constipation
- Facial features largely consistent

Figure 2: One of the two cases was referred to us for a second opinion following a prior diagnosis of PTHS, which we considered a misdiagnosis. The patient has a partial deletion of the *TCF4* gene encompassing exons 1–3 and the upstream region, spanning approximately 1.2 Mb. The facial phenotype is partially consistent, whereas the neurological phenotype is not.

10.50, WHAT LIES BEYOND PIERPONT SYNDROME? PHENOMIZING TBL1XR1-RELATED SPECTRUM

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Pierpont syndrome (OMIM #602342) is an ultra-rare (1 in 1,000,000 worldwide) neurodevelopmental disorder originally related to a recurrent missense variant in the *TBL1XR1* gene. It is characterized by hypotonia, global developmental delay with intellectual disability, facial dysmorphisms and distinctive palmar and plantar fat pads.

Since the first clinical description in 1998, *TBL1XR1*-related disorder phenotypes have expanded into a variable clinical spectrum, while genotype–phenotype correlations remain poorly defined because of the still limited number of reported cases. In addition, the significant clinical overlap with other neurodevelopmental and dysmorphic syndromes may further complicate diagnosis. These challenges highlight the need for a more detailed clinical and dysmorphological characterization of the *TBL1XR1*-related spectrum.

Starting from the cohort of paediatric patients with disorders of the epigenetic machinery followed over the years at Paediatric Genetics Clinic of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan, we collected data from 12 patients diagnosed with *TBL1XR1*-related syndrome.

Through systematic deep phenotyping, we characterised the dysmorphological and neurodevelopmental profile of our cohort, with attention to longitudinal progression and subtle but distinctive clinical features that often escape recognition in isolated case reports.

Leveraging *Face2Gene*, a comparison between the faces of our patients and previously reported cases revealed a recurrent gestalt resemblance to Kabuki syndrome (OMIM #147920). We further compared Pierpont patients carrying the recurrent p.Tyr446Cys variant with individuals harbouring other variants, with the aim of exploring possible genotype–phenotype correlations and identifying a mutation-specific facial gestalt profile. To deepen the overlap with Kabuki syndrome systematically, we constructed composite images of the faces of patients with *TBL1XR1* variants and those with *KMT2D* variants. Comparison of these images revealed a marked phenotypic overlap between the two conditions, particularly when patients with elongated palpebral fissures were selected from the *KMT2D* group. Given this notable facial and dysmorphic convergence, we also applied the Kabuki clinical score to our cohort to assess shared phenotypic features and potential areas of clinical convergence between the two conditions.

Our cohort analysis suggests a broader and more heterogeneous clinical spectrum than previously reported and may point to possible genotype–phenotype correlations linking specific *TBL1XR1* variants to variable neurodevelopmental and dysmorphic outcomes. These observations contribute to better delineating the *TBL1XR1*-related spectrum, improving earlier clinical recognition and tailored management strategies.

11.05, “OH YES, I HAVE AN OLDER BROTHER WITH MILD INTELLECTUAL DISABILITY...”

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With the growing trend toward increasingly early genetic testing in the perinatal period, a specific patient population presenting with syndromic features may be heading toward diagnostic extinction: young adults.

We typically see patients in this category either because they remain undiagnosed, or because they have been identified through the family history of couples followed during preconceptional or prenatal counseling.

A selection of recently diagnosed cases will be presented, with accompanying photographs, retracing the evolution of their clinical presentation.

11:20, HDR SYNDROME DUE TO GATA3 HAPLOINSUFFICIENCY: PHENOTYPIC AND MOLECULAR CHARACTERISATION OF THE LARGEST REPORTED COHORT

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Background: HDR syndrome (Hypoparathyroidism, sensorineural Deafness, Renal dysplasia; OMIM #146255) is a rare autosomal dominant disorder caused by *GATA3* haploinsufficiency. *GATA3* encodes a zinc-finger transcription factor essential for embryonic development of the inner ear, parathyroid glands, and urogenital tract. With approximately 260 cases reported worldwide, the full phenotypic spectrum of *GATA3* haploinsufficiency remains incompletely characterised, particularly regarding rare manifestations and long-term outcomes. We present the largest cohort of HDR individuals to date.

Methods: Retrospective multicentre study of 62 unreported individuals from 41 families, ascertained through three French molecular diagnostic laboratories (*GATA3* sequencing and array-CGH). Systematic phenotyping covered audiometry, calcium-phosphate metabolism, renal imaging and function, and additional congenital anomalies.

Results: The classical phenotypic hierarchy was confirmed: sensorineural hearing loss (95.1%), requiring bilateral cochlear implantation in 79% of cases; hypoparathyroidism (64.5%), with symptomatic presentations in 9.6%; and renal anomalies in 59.6%, ranging from structural malformations (unilateral hypoplasia/agenesis, bilateral hypoplasia, horseshoe kidney) to chronic kidney disease (19.3%) and end-stage renal disease (9.6%). Only 43.5% of individuals presented the complete triad, illustrating significant phenotypic variability. Developmental delay was noted in 24.1%, with confirmed intellectual disability restricted to individuals carrying large multi-gene deletions.

Molecular analysis identified 35 distinct pathogenic *GATA3* variants: 79% single nucleotide variants (SNV, including 26% missense variants clustering exclusively within the zinc-finger domains) and 21% copy number variants (CNV). No significant genotype-phenotype correlation was identified for the three classical features.

Additional congenital anomalies of the urogenital tract were identified in 14.5% of individuals, predominantly females, and will be discussed in the context of the developmental role of *GATA3* in urogenital organogenesis.

Conclusion: This large French cohort refines our understanding of the phenotypic and molecular spectrum of *GATA3* haploinsufficiency. The broad clinical variability, even within families sharing an identical variant, underlines the importance of systematic and multidisciplinary evaluation at diagnosis. The high frequency of additional urogenital anomalies warrants discussion of an expanded clinical screening for this syndrome.

11:35, THE MULTIFACETED PHENOTYPIC PROFILE OF NEUROFIBROMATOSIS TYPE 1 IN A FAMILY CARRYING THE NF1 P.GLY848GLU VARIANT: A CASE SERIES

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Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder caused by pathogenic variants in the *NF1* gene, encoding neurofibromin, a negative regulator of the RAS/MAPK pathway. While the diagnosis relies on established clinical criteria, atypical or incomplete phenotypes cause significant diagnostic challenges, particularly when cutaneous manifestations are subtle or absent.

We report a case series of a family carrying the heterozygous pathogenic variant c.2543G>A (p.Gly848Glu) in the *NF1* gene, with significantly different clinical phenotypes.

The proband, a 43-year-old male, presented with widespread subcutaneous lipomas and two café-au-lait macules (CALMs), not fulfilling the revised Legius diagnostic criteria. Spinal MRI revealed extensive bilateral nerve sheath tumors, and a large plexiform neurofibroma was confirmed histopathologically.

His eldest sister displayed a more recognizable NF1 phenotype with multiple CALMs, cutaneous neurofibromas, a cervical plexiform neurofibroma and Lisch nodules. A younger sister presented with multiple cervical lipomas without formal NF1 features.

The eldest sister's son carried both the familial variant and Klinefelter syndrome, with optic pathway glioma requiring surgical and chemotherapeutic treatment, sphenoid wing dysplasia, and axillary/inguinal freckling.

Across the family, marked intrafamilial phenotypic variability was observed, with spinal neurofibromatosis (SNF) as a prominent shared feature. The p.Gly848Glu variant, located in the 844-848 region of neurofibromin, is associated with severe NF1 phenotypes as SNF, plexiform neurofibromas, and skeletal anomalies.

This series illustrates that atypical cutaneous features, particularly lipomatosis in the absence of classic CALMs or cutaneous neurofibromas, should not preclude NF1 diagnosis when other suggestive findings are present.

The emerging overlap between SNF and spinal nerve enlargements reported in other RASopathies suggests that spinal manifestations may reflect a broader consequence of RAS/MAPK pathway dysregulation beyond NF1.

Further studies about codon 848 variants are needed to develop targeted therapeutic approaches.

11:45, PRENATAL CASE OF RIT1 MOSAIC VARIANT AND NEONATAL OUTCOME

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Herein, we report the prenatal diagnosis and the neonatal outcome of a unique case with a *RIT1* mosaic de novo variant. The child was born to a healthy non-consanguineous Caucasian couple. Family history was unremarkable. Combined first-trimester screening revealed low risk. The ultrasound scan (US) at 21weeks of gestation was normal, except for the presence of two choroid plexus cysts, which disappeared in subsequent US scans. At 26 weeks of gestation the amniotic fluid volume was at the upper limit. US scan at 31 weeks of gestation revealed a right hydrothorax, which was promptly treated by Intrauterine Thoraco-Amniotic shunting. Concomitantly, serological testing for infectious disease and amniocentesis were performed. No infectious or immune diseases were detected. Cytogenetic analysis revealed a normal karyotype and microarray. NGS analysis using a custom panel for RASopathy-

disorder genes detected a 4% mosaic pathogenic variant c.268A>G, p.(Met90Val) in the exon 5 of *RIT1* gene. The variant was de novo.

The child was born at 37 weeks of gestation by spontaneous vaginal delivery and admitted to the Neonatal Intensive Care Unit. Chest tube drainage confirmed chylothorax, Non-Invasive Ventilation was required. Abdominal, cerebral and cardiac ultrasound were normal. Clinical examination revealed a volumetric asymmetry of the lower limbs (right>left), a firm vascular malformation encompassing the right limb and gluteal region and abdominal telangiectasias. Dermatological and clinical genetic evaluation were requested. At 2.5 months of age, a biopsy of the vascular malformation was performed yielding normal histological findings. Treatment with Sirolimus was initiated resulting in a reduction of the and volumetric difference and improved consistency of the lesion with decreased chest tube output (Ozeki *et al.*, 2024; Nakajima *et al.*, 2025).

NGS analysis on peripheral blood and pleural liquid (coverage >500X, VAF 1-2%) did not detect the *RIT1* variant. High coverage NGS analysis on the biopsied tissue (coverage >500X, VAF 1-2%) confirmed the presence of the pathogenic *RIT1* variant, with an estimated mosaicism level of 9%.

This variant has previously been described at the germline level in prenatal cases presenting with fetal hydrops, bilateral severe chylothorax and minor facial anomalies, culminating in fetal demise (Miceikaite *et al.*, 2021; Qiu *et al.*, 2022).

However, the chylothorax recurred and progressed to diffuse bilateral pulmonary consolidation. Dynamic contrast enhanced Magnetic Resonance Lymphangiography revealed a complex central lymphatic flow disorder associated with bilateral pulmonary lymphatic perfusion syndrome.(Pieper *et al.*, 2022) The molecular diagnosis, along with the documented lymphatic abnormality allowed compassionate-use approval of Trametinib (Gazzin *et al.*, 2024). The treatment led to the chylothorax improvement, and the child was discharged from the hospital.

To our knowledge, our case represents the first clinical case of detection of a RIT1 mosaic variant, providing valuable insight into the severe phenotype associated with this variant. Furthermore, it emphasizes the importance of analyzing various tissues in newborns who present with atypical clinical manifestations of RASopathies. Improved identification of variants in the RAS/MAPK pathway, combined with a deeper understanding of genotype-phenotype correlations, could help further validate new targeted therapeutic strategies, making the clinical management of these patients more appropriate and timely, even in cases of rare mosaicism (Gazzin *et al.*, 2024).

11:55, SNAPC4-RELATED NEURODEVELOPMENTAL DISORDER DEFINES A STAGE-DEPENDENT SPLICEOSOMOPATHY WITH HETEROGENEOUS CLINICAL TRAJECTORIES

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Background: The small nuclear RNA-activating complex polypeptide 4 (SNAPC4) encodes the largest scaffolding subunit of the SNAPc complex, essential for transcription of spliceosomal small nuclear RNAs (snRNAs) by RNA polymerase II and III. Although pathogenic variants in *SNAPC4* have been associated with a rare neurodevelopmental disorder, the full phenotypic spectrum and underlying molecular mechanisms remain poorly defined.

Methods: We assembled an international cohort of 14 individuals harboring 18 distinct pathogenic *SNAPC4* variants and one multi-exon deletion, three of which had been previously reported, including frameshift, splice-site, multi-exon deletions, and missense alleles. Detailed clinical and neuroimaging data were integrated with *in silico* structural and protein–

protein interaction analyses to assess the impact of these variants on SNAPc architecture and function.

Results: *SNAPC4*-related disease emerges as a highly heterogeneous clinical continuum rather than a uniform progressive disorder. Core features included global developmental delay and microcephaly, with variable trajectories ranging from static cognitive impairment to adult-onset progressive motor dysfunction, alongside neurobehavioral phenotypes such as autism and ADHD. Neuroimaging revealed abnormalities suggestive of impaired neurogenesis and gliogenesis, including lissencephaly-pachygyria and hypomyelinating leukodystrophy. Structural modeling supports a unifying loss-of-function (LoF) mechanism, whereby variants destabilize the SNAPc complex or disrupt key interfaces required for DNA binding and RNA polymerase recruitment, consistent with impaired SNAPc function and transcriptional dysregulation.

Conclusion: These findings redefine *SNAPC4*-related disease as a stage-dependent neurodevelopmental spliceosomopathy, linking disruption of SNAPC4 to impaired SNAPc function and transcriptional dysregulation, with direct implications for diagnosis and variant interpretation.