# Program Booklet

## EuroNDD 2026

### Third European Workshop for a multidisciplinary view on rare genetic neurodevelopmental disorders

*April 9 - 10, 2026, Warsaw*

European Reference Networks
Co-funded by the Health Programme of the European Union
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# Program on Thursday April 9

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**Invited speakers**

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Helene Cederroth (SE)

9:15 – 9:45 **Touch and Tuberous Sclerosis Complex: what human and animal studies are teaching us**
Ewelina Knapska (PL)

9:45 – 10:15 **Precision medicine for monogenic epilepsies**
Gaetan Lesca (FR)

10:15 – 10:45 **"The road from diagnosis to intervention:**
**15 years of ENCORE Expertise Care for Angelman Syndrome"**
Karen Bindels de Heus (NL)

10:45 – 11:15 ***Coffee break***

11:15 – 12:30 **Parallel session 1 – Understanding the neurobiology**
Chairs: Zeynep Tümer (DK) & Agnieszka Madej Pilarzyk (PL)

11:15 – 11:30 NARS1 Variants in Neurodevelopmental Disorders Using, Xenopus tropicalis, Drosophila and Molecular Dynamics Simulations
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11:30 – 11:45 De novo variants in LDB1 are linked to distinct neurodevelopmental disorders depending on variant location and consequences
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11:45 – 12:00 Biological parameters in 100 girls with Rett syndrome: toward a better pathophysiological understanding and new therapeutic perspectives
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12:00 – 12:15 Expanding knowledge of ultra-rare CACNA2D2-related developmental and epileptic encephalopathy: insights from 33 individuals
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12:15 – 12:30 Biallelic rare variants in fat mass and obesity-associated (FTO) cause a variable developmental phenotype: A genotype-phenotype correlation
**Radhakrishnan Periyasamy** (CH)



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11:15 – 12:15 **Parallel session 2 – From molecular diagnostics to interventions**

Chairs: Gaetan Lesca (FR) & Marco Tartiglia

11:15 – 11:30 B2B-RARE: Bench to bedside in rare diseases
**Andreas Roos** (GER)

11:30 – 11:45 Modelling Tubulinopathies using human iPSCs-derived motor neurons
**Ilaria Svezia** (IT)

11:45 – 12:00 PURA Syndrome as Congenital Myasthenic Disorder. Evidence from Muscle Morphology, Proteomics and Blood Biomarkers
**Magdalena Mroczek** (PL)

12:00 – 12:15 Dissecting the Epigenetic Basis of USP7-Related Neurodevelopmental Disorders: From DNA Methylation Signatures to Chromatin Dysregulation
**Manasa Kalya Purushothama** (NL)

12:30 – 13:30 ***Lunch***

13:30 – 14:15 ***A guided poster tour***

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14:30 – 17:30 ***Parallel break-out sessions***
Supervised by event coordination team

14:30 – 15:45 **Topics of the first round**

1. Solving the undiagnosed: How recent insights translate into optimized workflows. **Katrin Ounap (EE), Helene Cederroth (SE), Zeynep Tümer (Dk), Tjitske Kleefstra (NL)**

2. Pain in people with intellectual disabilities: methodical and interdisciplinary collaboration (an educational session). **Leendert Sneep & Nanda de Knegt ( NL)**

3. From Guideline to Practice - Implementing ERN ITHACA Guidelines (an educational session) **Mirthe Klein Haneveld (NL), Agnies van Eeghen (NL) & co-workers cross Europe**

4. From Principles to Practice: Interprofessional Collaboration in Rare Genetic Intellectual Disability Syndromes – A European Round Table. **Mana Nasori, Kim Oostrom, Lotte Haverman, Sylvia Huisman (NL)**



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15:45 – 16:15 ***Exchange break with drinks & snacks***

16:15 – 17:30 **Second round topics**

1. Towards Precision Medicine for NDD. **Geatan Lesca (FR), Beatrice Desnous (FR), Adreas Roos (GER), Kasia Kotulska (PL)**

2. From training skills to enabling interactions: A new paradigm in AAC for individuals with neurodevelopmental disorders and complex communication needs (an educational session). **Gillian Townend (UK), Maartje ten Hooven-Radstaake (NL), Cindy Navis (NL), Paulina Rutka (PL), Elżbieta Dawidek (PL)**

3. Building Patient Registries under the GDPR – The Good, the Bad and the Ugly (an educational session followed by a roundtable discussion). **Christian Gebhard (GER), David Townend (UK)**

4. Neuropsychological insights: Cognition as a bridge between brain and behaviour in rare genetic syndromes? **Anja Bos-Roubos, Jennifer Kramer, Carmen Oldenboom, Ellen Wingbermühle, Jos Egger (NL)**

5. From Networks to Norms: Developing First European Recommendations and Care Principles for PIMD / Polyhandicap. **Sylvia Huisman (NL), Annette van der Putten (NL), Marie-Christine Rousseau (FR), Ilse H. Zaal-Schuller (NL)**

17:30 – 18:30 ***Optional time to discuss other matters in the available rooms.***
If you would like to do so, please let us know via info@in-act.nl

20:00 – 22:00 **Dinner. On registration only!**



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# Draft Program on Friday April 10

8:30 – 8:45 **Welcome & reflection on day 1**

8:45 – 10:15 **Plenary session 2:**
**From holistic (health)care networks towards systematic data capture**
Chairs: Christiane Zweier (CH) & Tjitske Kleefstra (NL)

**Invited speakers**

8:45 – 9:15 **Early interventions in intellectual disabilities associated with epilepsy: lessons from TSC**
Katarzyna Kotulska (PL)

9:15 – 9:45 **The transition process among (para)medics involved in the care network surrounding children with rare genetic neurodevelopmental disorders: the Single Bulgarian Expert centre expertise.**
Nikolinka Yordanova (BG)

9:45 – 10:15 **Rare disease discovery:**
**from molecular diagnosis to clinical intervention and care. Experience in Estonia**
Katrin Ounap (EE)

10:15 – 10:45 ***Coffee break***

10:45 – 12:00 **Plenary session 3:**
**Multidisciplinary diagnostics & interventions translated into a holistic (heath)care network**
Chairs: Laura de Graaff (NL) & Dorica Dan (RO)

10:45 – 11:00 Psychometric properties of a patient reported outcome measure (PROM) set for genetic intellectual disability
**Alannah Hijlkema** (NL)

11:00 - 11:15 Pain Assessment in Individuals with Profound Intellectual and Multiple Disabilities (PIMD/Polyhandicap): Evidence, Expert Opinion, and Caregiver Perspectives
**Ilse Zaal-Schuller** (NL)

11:15 – 11:30 A study on caregiver burden and quality of life of informal caregivers of children with metachromatic leukodystrophy in Poland
**Karolina Śledzińska** (PL)

11:30 - 11:45 The use of AAC in genetic syndromes; lessons learned during 10 years clinical practice
**Maartje Radstaake** (NL)

11:45 - 12:00 People with Profound Intellectual and Multiple Disabilities/Polyhandicap, Families, and Institutional Caregivers: The French EVAL-PLH Cohort. Results and Perspectives
**Marie Christine Rousseau** (FR)



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12:00 – 13:00 ***Lunch***

13:00 – 14:00 ***A guided poster tour***

14:00 – 14:15 ***Transition to the break-out sessions***

14:15 – 15:30 ***Parallel break-out sessions***
Supervised by event coordination team

14:15 – 15:30 **Third round topics**

1. Measuring what matters in genetic neurodevelopmental disorders: trials and care.
   **Agnies van Eeghen & Ellen Elsman (NL)**

2. Transition of Care for Adults with Intellectual Disabilities in Genetic Syndromes.
   **Nikolinka Yordanova(BU), Laura de Graaff (NL), Kasia Swieczkowska (PL)**

3. Communication support for individuals with neurodevelopmental disorders and complex communication needs: sharing best practices (a round table discussion). **Gillian Townend (UK), Maartje ten Hooven-Radstaake (NL), Cindy Navis (NL), Paulina Rutka (PL), Elżbieta Dawidek (PL)**

4. Pain in people with intellectual disabilities: implementation and network formation (a round table discussion). **Leendert Sneep & Nanda de Knegt (NL)**

15:30 – 15:45 **Final words**
Prof. Tjitske Kleefstra (NL), Prof. Christiane Zweier (CH), Prof. Alain Verloes (FR)



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# Plenary session 1 (Thursday April 9, 8:45 – 10:45)

*- Invited speakers –*

**The Undiagnosed Hackathon Model**

Helene Cederroth

Founder and President of the Wilhelm Foundation, an international non-profit dedicated to ending the diagnostic odyssey for People Living With Undiagnosed Diseases (PLWUD). She is a co-founder and permanent board member of the Undiagnosed Diseases Network International (UDNI). She also founded the Undiagnosed Hackathon and Global Undiagnosed Day (April 29).

An astounding 350 million people living with undiagnosed diseases (PLWUD) are scattered across the globe. They often endure long and complex diagnostic journeys characterised by uncertainty, fragmented care and limited access to specialised expertise. Despite rapid advances in genomics and data science, approximately 60% of individuals remain without a diagnosis, even after undergoing state-of-the-art investigations.

The Undiagnosed Hackathon Model was developed to address this critical issue by creating an intensive, collaborative and patient-centred diagnostic framework. Pioneered by the Wilhelm Foundation, the Undiagnosed Hackathon is a time-limited, multidisciplinary event that brings together clinicians, geneticists, bioinformaticians, data scientists, AI specialists, researchers and families.

Over a focused 48-hour period, teams work side by side to tackle complex clinical and genomic data, apply innovative analytical approaches and explore novel hypotheses that are not routinely accessible in standard clinical pathways. Families are actively involved, ensuring that lived experience and deep phenotyping inform every stage of the process.

The Undiagnosed Hackathon aims to find new solutions and collaborations to solve undiagnosed diseases.

**Touch and Tuberous Sclerosis Complex: what human and animal studies are teaching us**

Ewelina Knapska

Head of Neurobiology of Emotions Lab at Nencki Institute of Experimental Biology in Warsaw, Poland

Altered sensory processing, particularly atypical responses to touch, is a common but insufficiently understood feature of Tuberous Sclerosis Complex (TSC). In this talk, I will present converging evidence from human neuroimaging and mechanistic mouse studies suggesting that disrupted touch processing may form a foundation for social interaction difficulties in TSC. Resting-state and task-based fMRI data from adolescents with TSC reveal increased functional connectivity across sensory networks, together with a strongly diminished neural response during an affective touch paradigm. To explore potential mechanisms underlying these findings, we examined a mouse model with a postmitotic mutation of the *Tsc2* gene selectively in inhibitory neurons. These mice replicate key human findings, including increased connectivity between the thalamus and somatosensory cortex. Patch-clamp recordings from both regions in homozygous and heterozygous mutants demonstrate significant physiological alterations, consistent with impaired stimulus filtering and sensory gating. Crucially, these circuit-level abnormalities are accompanied by specific changes in social behavior, particularly behaviors that rely on touch. Together, these results support the idea that altered touch processing, driven by disrupted inhibitory control within thalamocortical circuits, may contribute directly to social interaction difficulties in individuals with TSC, with important implications for clinical assessment and intervention.



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## Precision medicine for monogenic epilepsies

Gaetan Lesca
Medical Genetics at University Claude Bernard in Lyon, France

Epileptic disorders are a highly heterogeneous group of neurological disorders, and a substantial proportion are now known to have a monogenic genetic basis, particularly in early-onset and severe forms. Advances in next-generation sequencing have led to the identification of pathogenic variants in more than hundred of genes, transforming both diagnosis and our understanding of disease mechanisms.

Among monogenic epilepsies, channelopathies play a central role. They result from mutations in genes encoding neuronal ion channels—such as sodium, potassium, calcium, or chloride channels—that are critical for regulating neuronal excitability. Variants in genes including *SCN1A*, *SCN2A*, *SCN8A*, *KCNQ2*, and *KCNT1* are associated with a wide clinical spectrum, ranging from self-limited neonatal epilepsies to severe, drug-resistant epileptic encephalopathies. Importantly, the functional impact of these mutations, whether loss or gain of function, strongly influences clinical presentation and treatment response.

We performed a monocentric study evaluates the real-life implementation of precision therapy in genetic epilepsies. In a retrospective cohort of 54 patients with variants in 18 genes, treatment was already adapted at diagnosis in most patients with *SCN1A* variants but in only a minority of others. Following genetic results, treatment was modified in 28% of patients, with clinical improvement in 60% of cases. These findings highlight the emerging but still limited impact of precision medicine in routine epilepsy care.

In the next years, genetic and functional characterization of variants will enable more rational therapeutic choices, including the use of targeted treatments in selected cases. Furthermore, the identification of treatable genetic epilepsies and the development of emerging gene- and RNA-based therapies.

## "The road from diagnosis to intervention: 15 years of ENCORE Expertise Care for Angelman Syndrome"

Karin Bindels de Heus
Pediatrician at the ENCORE Expertise center, Erasmus MC Sophia Childrens's Hospital in Rotterdam, the Netherlands

Our ENCORE Expertise center for Angelman Syndrome (AS) at the Erasmus MC Sophia Childrens's Hospital in Rotterdam, the Netherlands, started in 2010 and consists of a pediatrician, pediatric neurologist, specialized nurse, behavioral therapist, child- and youth psychiatrists, neuropsychologists, clinical geneticist, speech- and language therapist, physical therapist, dietician and physician for ID. We have seen around 200 children and 100 adults by now. We will present what we have learned in our 15 year journey on expertise care. The presentation will address successes and challenges in patient care and research. We will discuss the importance of standardized and multidisciplinary clinical care and natural history studies, the challenges of finding good and developing new outcome measures, the synergistic effect of combining pre- and clinical research, the persistent importance of clinical intervention studies beside the exciting development of targeted therapy and its trials, the enormous value of cooperation with parent organizations, our experiences of working together with pharmaceutical companies and the significance and future of a European AS network.

*- abstracts –*

## ID 84 ORAL PRESENTATION

### NARS1 Variants in Neurodevelopmental Disorders Using, Xenopus tropicalis, Drosophila and Molecular Dynamics Simulations

Yasemin Akın[1], Inci Sardag[1], Farzaneh Larti[1,2], Stephen Viviano[3], Nurdeniz Nalbant[4], Erdal Eren[5], Arzu Celik[1,2,6], Mahmut Cerkez Ergoren[7], Engin Deniz[3], Sebnem Ozemri Sag[8], Sehime G. Temel[4,8]

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**Introduction:** Asparaginyl-tRNA synthetase 1 (NARS1, MIM:108410) is a cytoplasmic Class IIa enzyme essential for protein synthesis. Mutations in NARS1 have been associated with both autosomal recessive and dominant neurodevelopmental disorders. The developmental suitability of Xenopus tropicalis and the strong evolutionary conservation of NARS1 with its Drosophila ortholog AsnRS make these organisms powerful in vivo systems for investigating disease mechanisms. Because the pathogenicity of many missense variants remains difficult to predict, we combined in vivo functional assays with molecular dynamics (MD) simulations to evaluate their biological and structural consequences.

**Methods:** We used Xenopus tropicalis and Drosophila melanogaster models to assess the developmental roles of NARS1. In Xenopus, in situ hybridization, CRISPR/Cas9-mediated knockdown, and OCT imaging were performed to examine neural development. In Drosophila, Nars1 disruption was analyzed by qRT-PCR, confocal microscopy, and MATLAB-based morphometric quantification. Additionally, all-atom molecular dynamics simulations were conducted under near-physiological conditions to investigate the structural effects of seven NARS1 missense variants (R11P, K60E, G132C, N221S, Y289C, L350P, and T459I).

**Results:** We identified a novel missense variant, Y289C, in a Turkish patient presenting with neurodevelopmental abnormalities. Loss of NARS1 function in Xenopus tropicalis led to microcephaly and neural tube defects, whereas Nars1 disruption in Drosophila caused epithelial remodeling defects resembling impaired neural tube closure. MD simulations revealed distinct conformational perturbations among the variants: Y289C and L350P disrupted the dimerization interface through structural rearrangements, while G132C and N221S appeared to compromise interdomain coordination and tRNA binding.

**Conclusion:** Our integrated in vivo and in silico analyses provide mechanistic insights into how NARS1 variants contribute to neurodevelopmental disorders and highlight distinct structural mechanisms underlying their pathogenicity.

**Keywords:** Aminoacyl-tRNA synthetase, Drosophila melanogaster, missense variants, molecular dynamics simulation, NARS1, neurodevelopmental disorders, Xenopus tropicalis.



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## ID 6 ORAL PRESENTATION

### De novo variants in LDB1 are linked to distinct neurodevelopmental disorders depending on variant location and consequences

Rebecca Fluri[1,2], Mireia Coll-Tané[3], Theresa Brunet[4], Benjamin Cogne[5], Solene Conrad[5], Mathilde Nizon[5], Francesco Nicita[6], Lorena Travaglini[7], Margie Glissmeyer[8], Amanda Peterson[8], Jillian G. Buchan[8], Dan Serber[8], Kolja Meier[9], Jutta Gärtner[9], Susann Diegmann[9], Veronique Pingault[10], Tania Attie-Bitach[10], Thomas Courtin[11], Michael C. Schneider[12], Wing Hung[12], Inderneel Sahai[13], Lauren O'Grady[13], Katharina Steindl[14], Sarju G. Mehta[15], Christel Depienne[16], Delphine Heron[17], Boris Keren[17], Solveig Heide[17], Shane McKee[18], Franco Laccone[19], Kristin G Monaghan[20], Catherine Melver[21], Connie Motter[21], Christiane Zweier[1,2], Anne Gregor[1,2]

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**Introduction:** LDB1 (lim domain binding 1) encodes a coregulator protein, which plays an important role in neurogenesis, and represents an essential binding partner of NDD-associate transcription factor LHX2. Few C-terminal likely gene disrupting (LGD) variants have been reported in the literature in individuals with congenital ventriculomegaly.

**Methods:** Through international collaboration, we now assembled a cohort of 15 individuals with de novo variants affecting various regions of LDB1. Functional analysis using cell-based models and Drosophila melanogaster were performed to elucidate molecular disease mechanisms.
Results: Ten of the identified variants affected the whole gene or the N-terminal dimerization domain (gene deletions, NMD-sensitive LGD or missense) and five variants affected only the C-terminus of LDB1 including the LIM binding domain (LID) (missense or NMD-escaping LGD variants). All individuals showed variable neurodevelopmental phenotypes, including developmental delay and behavioral anomalies, and in accordance with the literature, individuals with C-terminal variants additionally showed ventriculomegaly, establishing a genotype-phenotype correlation associated with LDB1 variants.
We analyzed wildtype and mutant LDB1 interaction capabilities with itself its interaction partner LHX2 in HEK 293 cells. We found that missense variants affecting the dimerization domain of LDB1 disturbed the self-dimerization potential of LDB1, likely leading to a loss of LDB1 function, while all C-terminal variants impaired the interaction of LDB1 with LHX2, likely in a dominant negative way.


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We also studied the consequences of LDB1 variants in Drosophila melanogaster in a LDB1/chip deficient background Pan-neural knockdown of the fly ortholog chip resulted in impaired locomotor behavior, also highlighting the importance of chip for nervous system function. This phenotype could be rescued by overexpressing wild type LDB1, but not by N-terminal missense variants, confirming their loss-of-function effect. In contrast, overexpression of LDB1 with the C-terminal LID missense variant led to an even stronger locomotor impairment compared to chip knockdown alone, confirming a dominant negative effect.

**Conclusion:** In summary, our findings link de novo variants in LDB1 to two overlapping, but distinct neurodevelopmental disorders based on their location, and highlight two distinct pathomechanisms of LDB1-related NDDs.

**Key words:** neurodevelopmental disorder, LDB1, disease modeling,Drosophila melanogaster, rare disease, genotype-phenotype correlation



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## ID 9 ORAL PRESENTATION

### Biological parameters in 100 girls with Rett syndrome: toward a better pathophysiological understanding and new therapeutic perspectives

Béatrice Desnous[1], Samuel Dahan[1], Jean-Christophe Roux[2], Federica Annichiarico[1], Magatte Fall[3], Robin Cloarec[1], Hully Marie[3], Bahi Buisson Nadia[3], Mathieu Milh[1]

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**Background:** Rett syndrome (RTT) is a rare neurodevelopmental encephalopathy caused by a pathogenic variant in the MECP2 gene and represents the leading genetic cause of profound intellectual and multiple disabilities (PIMD) in girls. The aim of this study was to identify biomarkers associated with clinical severity in RTT patients, reflecting disease dynamics and potentially guiding patient management.

**Methods:** This prospective bicentric study (2019–2024), conducted at La Timone Children's Hospital (Marseille) and Necker–Enfants Malades Hospital (Paris), included 84 female patients under 18 years of age with genetically confirmed RTT. Blood samples collected during routine follow-up were analyzed for erythrocyte morphology, iron metabolism, hemolysis markers, inflammation, lipid profile, and insulin signaling pathway components. Each patient was phenotyped using the Rett Clinical Severity Score.

**Results:** Earlier age at diagnosis ($p = 0.01$), severe malnutrition ($p = 0.03$), and the presence of a gastrostomy ($p = 0.02$) were associated with a more severe phenotype. Biologically, lower mean platelet volume ($p = 0.004$) and increased red cell anisocytosis ($p = 0.001$) also characterized the most severe RTT cases. Chronic systemic inflammation — reflected by elevated CRP ($p = 0.03$), complement fractions C3 ($p = 0.02$) and C4 ($p = 0.04$), and CH50 ($p = 0.02$) — was associated with both platelet activation, evidenced by thrombocytosis combined with reduced mean platelet volume ($r = –0.40$; $p = 0.017$), and altered erythropoiesis, leading to decreased hemoglobin levels ($r = –0.43$; $p < 0.001$) and increased anisocytosis ($r = 0.39$; $p = 0.019$).

**Discussion/Conclusion:** This exploratory study highlights potential biomarkers linking systemic inflammation, hematologic alterations, and clinical severity in RTT. Validation in longitudinal and control cohorts is warranted to establish clinically relevant thresholds for patient monitoring.

**Key words**: RTT, RETT syndrome, biomarker, clinical severity, PIMD

## ID 21 ORAL PRESENTATION

### Expanding knowledge of ultra-rare CACNA2D2-related developmental and epileptic encephalopathy: insights from 33 individuals

Miriam Essid[1,2,3,4], Sabrin Haddad[5], Justine Fraize[6], Olfa Jallouli[7], Javeria Raza Alvi[8], Somayeh Bakhtiari[9,10], Meriem Ben Hafsa[1,2], Hanene Benrhouma[1,2], Wafa Bouchaala[7], Rahel Burger[11], Edvin Cai[12], Prem Chand[13], Nicolas Chatron[3,4], Hossein Darvish[14], Stephanie Efthymiou[12], Carolina Isabel Galaz Montoya[9,10,15], Shahzad Haider[16], Henry Houlden[12], Musharraf Jelani[17], Hamza Khan[18], Ichraf Kraoua[1,2], Michael C. Kruer[9,10], Reza Maroofian[12], Erik Riesch[19], Damien Sanlaville[3,4] , An-Sofie Schoonjans[20],Go Hun Seo[21], Hannah Stamberger[20], Tipu Sultan[8], Chahnez triki[7], Dorothée Ville[6], Barbara Vona[22,23], Qaiser Zaman[18,24], Steffen Zuchner[25], Sara Cabet[4], Clarissa Eibl[5], Gerald J. Obermair[5], Gaetan Lesca[3,4]

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**Background:** Developmental and epileptic encephalopathy (DEE) associated with CACNA2D2 variants is an ultra-rare autosomal recessive disorder. The few reported cases share strikingly phenotypic similarities. CACNA2D2, predominantly expressed in the cerebellum, encodes the α2δ-2 subunit of voltage-gated calcium channels (VGCC). It regulates channel membrane trafficking and current properties. Our study aims to expand the clinical description through analysis of a large case series, and to assess the functional impact of relevant CACNA2D2 variants.

**Methods:** Through GeneMatcher, ERN-EpiCARE and international collaborations, we assembled individuals carrying biallelic CACNA2D2 variants. Clinical data were collected through a standardized survey. Brain MRI files were re-



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analysed. Functional characterization, including minigene assays and heterologous and homologous protein expression analysis of novel variants were performed.

**Results:** Clinical and genetic data were collected from 22 newly reported individuals and 11 previously published cases, all carrying CACNA2D2 variants. The core features included early-onset drug-resistant epilepsy starting at a median age of 4 months (20 days–4 years), axial hypotonia (100%), severe cognitive and motor impairment (100%), and progressive cerebellar atrophy (70%). Additional signs observed included movement disorders (86%), mainly generalized dystonia, nystagmus (54%), and Ataxia (32%).
Epilepsy demonstrated age-dependent improvement and significant quadriparesis became more evident (54%).
Molecular analysis revealed 20 CACNA2D2 variants, including 12 null variants, 6 splice site variants, 3 nonsense variants, and 3 deletions, and 8 missense variants. All identified variants were absent in biallelic state and exhibited extremely low allele frequencies in monoallelic state in population databases. Functional studies demonstrated distinct pathophysiological mechanisms. Missense variants affect the functioning of VGCC and alter synaptic transmission while truncating variants are likely triggering nonsense-mediated RNA decay, resulting in a complete loss of the protein. Our data predict that aberrant expression of α2δ-2 disrupts the excitatory-inhibitory synaptic balance, a key mechanism underlying neurodevelopmental disorders.

**Conclusion:** Our findings strengthen the role of CACNA2D2 in DEE and highlight the dual pathogenic mechanisms underlying this disorder, encompassing both channelopathy and synaptopathy.

## ID 9 ORAL PRESENTATION

### Biallelic rare variants in fat mass and obesity-associated (FTO) cause a variable developmental phenotype: A genotype-phenotype correlation

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**Introduction:** Fat Mass and Obesity-Associated (FTO), a Fe(II)-and 2-oxoglutarate (2OG)-dependent oxygenase, is an RNA demethylase that mediates oxidative demethylation and regulates fat mass, adipogenesis, and energy homeostasis. Specifically, it demethylates N(6)-methyladenosine RNA and affects the mRNA expression and stability. SNP risk alleles in FTO have been described for obesity, type 2 diabetes, and cardiovascular and neuropsychiatric disorders. A limited number of reports document biallelic rare coding variants in FTO as the cause of developmental phenotypes, including severe growth retardation and multiple malformations.

**Patients and methods:** We initially found two siblings from an Indian family with global developmental delay and severe growth retardation with a bi-allelic variant in FTO (NM_001080432.3). Through personal communications and connecting with the European Reference Network on Rare Congenital Malformations and Rare Intellectual Disability ERN-ITHACA, we collected additional eight patients from six families. We review phenotype and genotype correlations from published cases (13 individuals from four families) and patients from our series. Index patients from our families underwent detailed clinical and radiological examination followed by exome/genome sequencing.

**Results:** We identified ten patients from seven families of Indian (families 1-5) and European descent (families 6-7) with biallelic variants in FTO. A recurring (presumably founder) novel homozygous variant was found in seven patients (families 1-4) who were from the same geographic region in India. Family 5 carried a novel stop codon variant. Families 6 and 7 carried previously reported bi-allelic variants. A total of five variants have been reported, which were clustered at the catalytic N-terminal domain of FTO, specifically at Fe(II)/2OG active sites. Patients carrying variants at this site had severe growth retardation, brain anomalies such as cortical atrophy, lissencephaly, Dandy-Walker malformation and ventriculomegaly, cardiac anomalies, dysmorphism, and early lethality. The founder variant that we identified in our cohort is situated outside the active site and is highly conserved. These individuals manifest developmental symptoms that are less severe without any structural brain anomaly and no early lethality. Conversely, the stop codon variant in family 5, which is situated at the active site, causes severe developmental anomalies as early as 22 weeks of gestation. IUGR, polyhydramnios, defective gyration, and cysts were common prenatal findings in our patient series.

**Conclusion:** We describe a series of ten patients and review published cases, including the first documentation of the prenatal phenotype of FTO variants, thereby expanding the spectrum of FTO-related developmental anomalies. Variants in the 2OG-binding sites of FTO are expected to inactivate the enzyme, resulting in severe manifestations, but alterations in other conserved residues within the catalytic domain preserve some residual function of FTO, leading to milder developmental abnormalities. This phenotype-genotype expansion may facilitate counselling on prognosis and informed decision-making.

**Keywords:** growth retardation, developmental delay, founder mutation, FTO-demethylase

# Parallel session 2 – From molecular diagnostics to interventions (Thursday April 9, 11:15 – 12:15)

*- abstracts –*

## ID 31 ORAL PRESENTATION

### B2B-RARE: Bench to bedside in rare diseases

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**Introduction:** Neurodevelopmental disorders (NDDs) are rare diseases that may impact a patient's cognitive, social, emotional, and motor development, often leading to lifelong challenges in learning, behavior, or daily functioning. Many NDDs may be complicated by additional clinical features such as neuromuscular symptoms. For many of these complex phenotypes, there are no therapeutic options, highlighting the urgent need for innovative approaches to diagnostics and treatment. Our EU-funded consortium project "B2B-RARE" aims to address this issue by developing marketable diagnostic and therapeutic methods to improve the care of NDD patients.

**Methods:** As part of an interdisciplinary approach, skin biopsies are collected from 120 patients with hereditary NMDs for fibroblast isolation and subsequent multi-omics analysis (Transcriptomics, Proteomics, and Metabolomics). Additionally, in selected samples, the density of intraepidermal nerve fibers is analyzed. Bioinformatics evaluations, supported by Artificial Intelligence (AI), will link the results of the multi-omics analyses with drug databases to identify potential therapeutic approaches. These therapeutic candidates, once the pathophysiologies are verified, will first be tested in preclinical fibroblast models. The pathophysiological relevance of the uncovered and therapeutically relevant pathomechanisms will then be validated through single nuclei sequencing of skin biopsies, with a focus on the arrector pili muscle and small nerve cells. Once this verification is complete, new therapeutic intervention concepts will be tested in individualized trials.

**Results:** The project has already led to the successful identification of initial therapeutic intervention targets for neuropathic diseases. A key example is patients with PPP1R21-related NDD with hypotonia, facial dysmorphism, and brain abnormalities (NEDHFBA), where our multi-omics approach revealed perturbed protein processing and clearance, cytoskeletal changes and dysregulation of neurological relevant proteins as major pathophysiological driver. Preclinical interventions with Metformin in patient-derived fibroblasts demonstrated significant improvements, restoring cellular fitness and correcting the protein dysregulations. Following this, an individualized treatment strategy using Metformin is currently initiated.

**Discussion/Conclusion:** B2B-RARE represents a significant step forward in improving the diagnosis and treatment of hereditary neuromuscular diseases. By utilizing skin biopsies as a minimally invasive diagnostic technique, the project aims to establish new pathways for treating rare diseases and ultimately enhance the quality of life for affected patients. The personalized therapeutic strategies developed through this project have the potential to optimize the care of hereditary NDDs and provide valuable insights that may be applicable to other rare diseases as well. The success of this project was paradigmatically demonstrated in PPP1R21-related NEDHFBA.

**Keywords:** Neurodevelopmental diseases (NDDs), Multi-omics analysis, Fibroblast as in vitro system, Personalized therapy, Single-nuclei sequencing

## ID 39 ORAL PRESENTATION

### Modelling Tubulinopathies using human iPSCs-derived motor neurons

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**Introduction:** Tubulinopathies represent a heterogeneous group of rare neurodevelopmental and neurodegenerative disorders caused by pathogenic variants in tubulin genes, which encode the structural units of microtubules. Microtubules play a critical role in neuronal functions like differentiation, axonal growth, and intracellular transport. Despite tubulinopathies clinical impact, there is a lack of effective treatments and the mechanisms by which tubulin variants differentially affect neuronal development or lead to neurodegeneration remain poorly understood. This study investigates the molecular mechanisms of two novel TUBB2A gene mutations, which result in distinct clinical phenotypes: one causing a neurodegenerative condition characterized by sensory-motor peripheral neuropathy, and the other leading to structural brain malformations.

**Methods:** Induced pluripotent stem cells (iPSCs) were generated from fibroblasts of patients carrying TUBB2A mutations. The iPSCs were confirmed to exhibit normal karyotype. Pluripotency markers expression was assessed by immunocytochemistry and RT-qPCR. Sanger sequencing confirmed the presence of the heterozygous TUBB2A variants in the respective cell lines. To evaluate the impact on microtubules dynamics, live-cell imaging was performed using nocodazole treatment to induce microtubule depolymerization and SiR-tubulin probe to monitor repolymerization. Control and mutated iPSCs were subsequently differentiated into spinal motor neurons (MNs). MNs were tested and evaluated as positive for appropriate pan-neuronal, pre- and post-synaptic, and motor neuron-specific markers.

**Results:** Live-cell imaging showed delayed microtubule reassembly in patient-derived iPSCs, particularly in the variant linked to neurodegeneration. Upon differentiation into MNs, mutant cells exhibited significant alterations in axonal fasciculation, neuronal clustering, and a reduction in neurite intersections, when compared to control. The mutation associated with brain malformations led to more relevant alterations, with neuronal somata clustering and axonal bundles of increased caliber, suggesting impaired neuronal organization.

**Conclusions:** Our findings provide novel insights into the molecular mechanisms of tubulinopathies, linking specific TUBB2A mutations to altered microtubule dynamics and neuronal architecture. Our iPSC-based MNs model offers a platform for dissecting disease mechanisms and may represent a valuable support for the development of targeted therapies for both neurodevelopmental and neurodegenerative forms of tubulinopathies.

**Key words:** tubulinopathies, TUBB2A, microtubule dynamics, neurodevelopmental disorders, neurodegenerative disorders, iPSCs, motor neurons differentiation.



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## ID 41 ORAL PRESENTATION

### PURA Syndrome as Congenital Myasthenic Disorder. Evidence from Muscle Morphology, Proteomics and Blood Biomarkers

Magdalena Mroczek[1,2], Corinna Preusse[3,4,5], Andreas Hentschel[6], Magdalena Chrościńska-Krawczyk[7], Michał Bielak[7], Adela Sobolewska[7], Adela Della Marina[8], Anisa Hila[9], Stanley Iyadurai[10], Florian Kraft[11], Venkatesh Kumar Chetty[9], David Muhmann[8], Tobias Ruck[12], Hans-Hilmar Goebel[3], Ulrike Schara-Schmidt[8], Vera Dobelmann[12], Basant Kumar Thakur[9], Werner Stenzel*[3], Andreas Roos[8,*]

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**Introduction:** Dominant PURA variants (encoding purine-rich element-binding protein A; OMIM#600473) cause a neurodevelopmental disorder with hypotonia, cognitive impairment, and variable neuromuscular symptoms. Clinical response to pyridostigmine suggests neuromuscular junction (NMJ) involvement, but NMJ architecture, molecular mechanisms, and minimally invasive biomarkers remain unclear. This study investigated NMJ pathology in PURA-patients using integrated clinical, histological, ultrastructural, and molecular approaches.

**Methods:** Ten genetically confirmed patients underwent detailed phenotyping with emphasis on congenital myasthenic syndrome (CMS)-like features. Quadriceps biopsy from one patient was analyzed by histology, immunohistochemistry, and electron microscopy. Proteomic profiling of muscle, serum, and extracellular vesicles (EVs) was performed by ELISA and mass spectrometry, with validation by qPCR.

**Results:** Patients presented with hypotonia, ptosis, ocular weakness, and myopathic facies, consistent with impaired neuromuscular transmission. Electron microscopy revealed vesicle accumulation and NMJ alterations, providing the first ultrastructural evidence of NMJ pathology in PURA. Muscle proteomics showed reduced PURA protein and dysregulation of transcriptional regulation, vesicle transport, extracellular matrix remodeling, and complement activation. qPCR confirmed POSTN and PHGDH upregulation among others. Serum analyses demonstrated elevated TSP4, identifying a candidateblood biomarker for PURA-associated NMJ dysfunction. EV proteomics revealed dysregulated immunoglobulins, complement components, and novel candidates including NOTCH2, TARSH, and PON1.

**Discussion/Conclusions:** Pathogenic PURA variants may impair NMJ structure and vesicle homeostasis, potentially linking molecular and ultrastructural defects with clinical myasthenic features and pyridostigmine responsiveness. Identification of TSP4 and EV-associated proteins as ‘minimally invasive biomarkers’ establish a framework for monitoring NMJ dysfunction in PURA disease and supports recognition of PURA-CMS as a distinct neuromuscular phenotype within the broader PURA spectrum.

**Key words:** PURA Syndrome, PURA-CMS, congenital myasthenic syndrome

## ID 42 ORAL PRESENTATION

### Dissecting the Epigenetic Basis of USP7-Related Neurodevelopmental Disorders: From DNA Methylation Signatures to Chromatin Dysregulation

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**Background and Objective:** Pathogenic variants in USP7 cause Hao-Fountain syndrome (HAFOUS), a rare neurodevelopmental disorder characterized by intellectual disability, developmental delay, hypotonia, and behavioral abnormalities. USP7 encodes a deubiquitinase that regulates protein stability and chromatin- associated complexes, positioning it as a key modulator of epigenetic homeostasis. However, how USP7 dysfunction disturbs chromatin organization and developmental gene regulation remains poorly understood. This study aimed to determine how USP7 deficiency reshapes the epigenetic and transcriptional landscape in patient-derived fibroblasts and whether these somatic cells retain persistent “epigenetic echoes” of early developmental disruption.

**Methods:** Primary dermal fibroblasts from four affected individuals and four matched controls were profiled using genome-wide DNA methylation and RNA sequencing. Integrated methylation–expression (eQTM) and pathway-enrichment analyses were used to identify coordinated regulatory disruptions.

**Results:** USP7-deficient fibroblasts exhibited 1,013 differentially methylated regions (~62% hypermethylated) and 310 differentially expressed genes enriched in neurodevelopmental pathways. Methylation and expression changes strongly converged on HOX clusters and other developmental regulators, suggesting a shift from poised to stably repressed chromatin states. The identified DNA-methylation signatures robustly distinguished USP7-related cases from controls, supporting an “epigenetic echo” model of disease.
Ongoing and Future Work:
To uncover the upstream chromatin mechanisms, ChIP-seq profiling of H3K27me3, H2AK119ub, and Pan-H3 is underway to define how USP7 loss disrupts Polycomb-mediated chromatin repression and nucleosome organization.

**Impact:** This work bridges gene expression, DNA methylation, and chromatin architecture, providing the first mechanistic framework for USP7-related NDD. Beyond USP7, it exemplifies how multi-omics dissection of rare NDDs can uncover shared regulatory pathways and inform future precision therapeutic strategies for early-onset intellectual disability.

**Key words:** USP7, Hao-Fountain syndrome, fibroblasts, DNA methylation, bivalency, eQTM, neurodevelopmental disorders, epigenetic dysregulation



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# Plenary session 2 (Friday April 10, 8:45 – 10:15)

*- Invited speakers –*

**Early interventions in intellectual disabilities associated with epilepsy: lessons from TSC**

Katarzyna Kotulska
Department of Neurology and Epileptology, The Children's Memorial Health Institute, Poland

Epilepsy, especially early childhood epilepsy, is associated with a significant risk of intellectual disability. In Tuberous Sclerosis Complex (TSC), a disease affecting 1 in 6,000 newborns and characterized by 90% risk of epilepsy, intellectual disability is present in about 60% of individuals. Due to the prenatal development of cardiac tumors in the majority of patients with TSC, the disease is increasingly diagnosed before birth, enabling the interventions before the onset of seizures. It is well established that interictal epileptiform discharges on EEG precede the onset of seizures and thus EEG can be used as a biomarker of developing epilepsy in TSC infants. Recent studies showed that early diagnosis and pre-emptive antiseizure treatment reduce the risk and severity of seizures, and might also decrease the risk of intellectual disability in children with TSC. Given that TSC results from inactivating mutations in either TSC1 or TSC2 genes, which downregulate the activity of mTOR pathway, new trials using preventive mTOR inhibitors were proposed and are currently ongoing.

**The transition process among (para)medics involved in the care network surrounding children with rare genetic neurodevelopmental disorders: the Single Bulgarian Expert centre expertise.**

Nikolinka Yordanova[1], Savi Shishkov[2], Violeta Iotova[1]
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The transition from paediatric to adult endocrine care represents a critical phase for patients with rare and chronic endocrine disorders, especially those with mental disabilities. In Bulgaria this process is still at an early stage of development. Between 2021 and 2025, a total of 53 patients with various rare endocrine disorders were transitioned in our centre (range 18–37 years). Of these 18.8% (7 with Prader–Willi syndrome, 1 with adrenoleukodystrophy, and 2 with maple syrup urine disease) can be classified as having confirmed intellectual disability
The aim of this presentation is to highlight the challenges in the transition process, the measures undertaken, and the future plans for improving this process from the perspective of the experience of the Varna Expert Centre for Rare Endocrine Diseases.
Current efforts are focused on identifying key gaps in the transition process, including the lack of nationally accepted transition guidelines, delayed transfer, insufficient coordination between specialists, inadequate patient preparedness, absence of unified medical records, underfunding, and fragmented care pathways. Current actions include joint consultations, psychological support, and the planned implementation of structured questionnaires to assess transition readiness. Future efforts will focus on international training initiatives, collaborative projects, and dissemination of experience, with the aim of supporting the development of a structured national transition model in Bulgaria.


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## Rare disease discovery: from molecular diagnosis to clinical intervention and care. Experience in Estonia

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More than 10,000 rare diseases (RD) are known to date, and about 80 % of RD have a genetic etiology. The average time to an accurate diagnosis of an RD is about 4–5 years, but in some cases it can take over a decade. Most patients suffering from an undiagnosed RD receive only symptomatic treatment. An accurate diagnosis can lead to better disease management, the identification of potential therapeutics, and the avoidance of unnecessary treatments with severe side effects.

To increase the diagnostic rate of RD in Estonia, in 2017, we first implemented exome reanalysis (ES) and short-read genome sequencing (GS) in cooperation with the Broad Institute, MIT, and Harvard, using the Seqr reanalysis program. Our research experience has shown that there is a continuous need to reanalyze ES data to increase diagnostic yield. GS identified diagnostic variants in an additional 8% of patients. In the second step in 2019, we performed RNA-sequencing (transcriptomics) to validate candidate splice-disrupting variants and identify splice-altering variants in both exonic and deep intronic regions. Our data showed that GS and RNA-seq, alone or in combination, achieved an additional diagnostic efficacy of 15%. Thirdly, we implemented an untargeted metabolomics analysis measure, measuring more than 800 compounds. Our team has focused on the detection of new RD and finding out similarities in the metabolic profiles of patients with epilepsy despite different etiology, seizure frequency, seizure type, and patient age. Significant differences ($p$-value $< 0.05$) were detected in the pediatric RD cohort with epilepsy across eight metabolites, mainly lipids. Metabolome data added special input in at least two cases for RD discovery. As a summary, using this combined approach, our diagnostic yield increased by at least twofold. In a clinical setting in Estonia, the efficacy of ES is 29%. In a research study, an additional 1/3 of previously unsolved cases received a genetic diagnosis, with the total diagnostic yield reaching approximately 70%. Our results highlight the importance of regular reanalysis of ES data, as 40% of cases were solved by reanalysis and implementation of different omics analyses.

Estonian Research Council grant PRG2040.

# Plenary session 3 – Multidisciplinary diagnostics & interventions translated into a holistic (heath)care network (Friday April 10, 10:45 – 12:00)

*- abstracts -*

## ID 46 ORAL PRESENTATION

### Psychometric properties of a patient reported outcome measure (PROM) set for genetic intellectual disability

Alannah R. Hijlkema[1,2,3,4], Nadia Y. van Silfhout[1,2,3,4], Ellen B. M. Elsman[1,2,3,7], Maud M. van Muilekom[1,3,5], Clara D. van Karnebeek[2,4,5], Lotte Kleinendorst[2,4,5], Michiel A.J. Luijten[1,3,4], Lotte Haverman[1,3*], Agnies M. van Eeghen[2,3,4,5,6*]
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**Introduction** Individuals with intellectual disabilities represent 1-3% of the population, with a large proportion attributable to genetic causes, collectively referred to as genetic intellectual disabilities (GID). The impact of GID can be substantial on daily life of affected individuals. Thus far, no comprehensive patient-reported outcome measure (PROM) set for GID exists. In order to address this gap, a generic core PROM set for children and adults with GID was developed. This study aims to evaluate the psychometric properties of the core PROM set in a Dutch sample of adults with GID, caregivers of children with GID and caregivers of adults with GID.

**Methods** Adults with GID, caregivers of children with GID, and caregivers of adults with GID were invited to participate in this study. Participants were asked to complete the generic core PROM set, primarily comprised of PROMIS item banks administered as computerized adaptive tests (CATs) or short forms, and legacy subscales at baseline (T0) and after two weeks (T1). Psychometric properties were assessed including evaluation of reliability (standard error (SE), internal consistency, test-retest), efficiency (items completed, floor and ceiling effects, and mean items completed), and construct validity (convergent and known-group validity). GID outcomes were expressed as mean T-scores and compared with Dutch or U.S. reference data.

**Results** Most PROMIS CATs and short forms showed sufficient reliability and efficiency for adults and caregivers of both children and adults, whereas the reliability of single-item PROMs varied. No floor or ceiling effects were observed for PROMIS CATs and short forms. Also, most hypotheses regarding convergent validity were confirmed, although some correlations were lower than expected.

**Conclusion** Preliminary findings suggest that the generic core PROM set demonstrates sufficient psychometric properties and is suitable for use among individuals with GID and their caregivers.

**Key words:** Intellectual disability, validation, psychometrics

## ID 57 ORAL PRESENTATION

### Pain Assessment in Individuals with Profound Intellectual and Multiple Disabilities (PIMD/Polyhandicap): Evidence, Expert Opinion, and Caregiver Perspectives

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**Introduction:** Pain is a multidimensional sensory and emotional experience that is influenced to varying degrees by biological, psychological, and social factors. (IASP). Individuals with profound intellectual and multiple disabilities (PIMD/polyhandicap; IQ < 25, GMFCS level V) face unique challenges in pain perception and assessment due to cognitive, motor, and communication impairments. They are at high risk of chronic pain from spasticity, musculoskeletal deformities, gastrointestinal disorders, and recurrent infections. Self-report is generally impossible, requiring reliance on behavioral and physiological cues such as facial expressions, posture, and autonomic changes.

**Methods:** A literature review was conducted to identify best practices for assessing pain source and intensity in people with PIMD/polyhandicap. Inclusion criteria were broadened to include individuals with IQ < 25 and severe motor impairment or severe cerebral palsy. Studies published between 2000 and 2022 focusing on behavioral, physiological, or caregiver-based pain assessment were included. The review was complemented by expert opinion to provide practical guidance on clinical assessment and intervention.

**Results:** Only one study met the inclusion criteria: a pilot validation of the Pain Behaviour Checklist (PBC) in 32 individuals with PIMD/polyhandicap, rated as medium quality (50%) using the JBI checklist. Limitations included reliance on the Visual Analogue Scale as a gold standard, unmeasured confounders, and incomplete reporting on IQ and pain-provoking conditions. The PBC showed satisfactory reliability (interrater = .63; intrarater = .88) and good validity for children (.75) but insufficient validity for adults (.28), and it is no longer officially available or translated into English, highlighting the scarcity of validated, population-specific tools. Expert consensus emphasized structured, multidisciplinary assessment, integrating proxy information, behavioral observation, physical examination, and trial treatment. Families and Direct Support Professionals are crucial in signaling pain, and a biopsychosocial approach is recommended for chronic pain. Key recommendations include timely analgesic intervention, tailored physical therapy, regular health checks, and collaborative networks for training and best-practice sharing.

**Discussion:** Implementing a biopsychosocial approach to chronic pain in individuals with profound intellectual and multiple disabilities (PIMD) is challenging due to cognitive and communication impairments. Mapping biopsychosocial factors is essential for personalized treatment, and practical strategies are needed to support clinicians, families, and caregivers. The literature review revealed very few studies on pain in PIMD, underscoring the need for evidence-based guidance. European collaboration is both necessary and beneficial to develop robust guidelines and support their implementation. This session will be conducted as an interactive working group, allowing participants to discuss strategies for initiating international cooperation and sharing best practices.

**Conclusion:** Evidence for pain assessment in PIMD/polyhandicap is limited. Combining expert guidance, caregiver input, and individualized approaches is crucial to improve recognition, diagnosis, and management of pain in this vulnerable population. There is urgent need for multicenter studies on pain assessment and treatment with the inclusion of pediatric and adult individuals.

**Key-words:** Profound Intellectual and Multiple Disabilities (PIMD/Polyhandicap), Pain Assessment, Behavioral Observation, Caregiver and proxy involvement, Multidisciplinary Approach, Biopsychosocial model of pain



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## ID 59 ORAL PRESENTATION

### A study on caregiver burden and quality of life of informal caregivers of children with metachromatic leukodystrophy in Poland

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**Background:** Metachromatic leukodystrophy (MLD) is a rare, inherited lysosomal storage disorder caused by a deficiency in arylsulfatase A (ARSA), leading to sulfatide accumulation, demyelination, and progressive neurological decline. Without treatment, patients – particularly those with early-onset forms – typically lose the ability to walk or communicate within months of symptom onset, and life expectancy is markedly reduced, often below 10 years. Although MLD is likely underdiagnosed in Poland, prevalence may be higher than average. Early diagnosis and prompt intervention with gene therapy (arsa-cel) are critical, as neuronal damage is irreversible. This study aimed to characterize the clinical course of MLD in Poland and assess the quality of life and financial well-being of caregivers.

**Results:** The study included 13 MLD patients and 28 caregivers. The most common forms were late-infantile (46.2%) and early-juvenile (38.5%). Most patients were classified as GMFC-MLD stage 6 (53.8%) and ELFC-MLD stage 4 (69.2%). Common symptoms included spasticity (84.6%), walking difficulties (84.6%), and speech disorders (69.2%). The mean age at diagnosis was 4.8 years, with 69.2% of caregivers reporting that delayed diagnosis adversely impacted the child's health. Caregivers were predominantly female (67.9%) and reported high caregiving demands (mean = 35.7 hours/week). WHOQOL-BREF scores exceeded medians for caregivers of people with rare diseases across all domains. Financial well-being was strongly correlated with physical ($r = 0.636$, $p < 0.001$) and psychological ($r = 0.717$, $p < 0.001$) quality of life. Only 14.3% of MLD caregivers received psychological counseling at diagnosis, though 92.3% received financial support. Gene therapy was reported in 15.4% of cases; most patients received multiple forms of rehabilitative therapy.

**Conclusion:** MLD in Poland is characterized by early-onset, rapidly progressing forms that lead to severe disability and impose significant burdens on families. Delayed diagnosis remains a pervasive issue, limiting access to potentially life-altering treatments. Despite intensive caregiving responsibilities, many caregivers report relatively preserved quality of life, especially when financial support is available. These findings highlight the urgent need for systematic newborn screening in Poland to facilitate early diagnosis and timely access to gene therapy, which could significantly improve patient outcomes and reduce the long-term burden on families and the healthcare system.

**Keywords:** caregiver burden; family caregivers; metachromatic leukodystrophy; parents experiences; quality of life.

## ID 66 ORAL PRESENTATION

### The use of AAC in genetic syndromes; lessons learned during 10 years clinical practice

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**Introduction & method:** AAC has taken an enormous journey the past several years. From PECS, to gestures to eye gaze computers to everything in between. We have seen it all and learned a lot about what does and what does not work. We believe that what we've learned is both universal and syndrome specific. During this workshop we will share insights and tap into uncharted territory. We will compare our insights to paradigm shifts in recent scientific literature concerning how to address AAC and AAC users, generally constituting a more holistic and dynamic view on human development and the innate need to connect.

**Results:** We've encountered more than 200 children and adults with Angelman syndrome and Dup15q syndrome, and their families. They've shown us that they communicate and make contact in several ways, but these ways may not fit our expectations or ideas of "normal or appropriate behavior". They preferably do not answer our questions or show us their knowledge when this is asked. They do, however, make jokes on their own terms, give you clear looks when you discuss topics that are important to them and/or use gestalts to voice out their opinions. They can find "*Sinterklaas*" in our speech computer when it is hidden five folders away and quickly use pictograms like "*You are a monster*" or "*That stinks!*" when we model them. They also make natural enhanced gestures (Calculator, 2002), vocalizations and hand you the remote when they want to watch TV. They rely heavily on their communication partners to construct a meaningful message out of this idiosyncratic potpourri of communicative behaviors.

We will discuss a shift from single-minded SMART goals to participation goals, in light of the UN Convention of the Rights of Persons with Disabilities and the Participation Model (Beukelman & Miranda, 2005). We've experienced the importance of all four Communication Competence domains (Light & McNaughton, 2014) and the necessity of modelling (Sennott, Light & McNaughton, 2016). But we've also learned a lot about the strain this puts on parents, the wider social network and the children themselves (Moorcroft et al., 2019a, 2019b) and the preference of many children on using their body language instead of their AAC device. This latter point is in contrast with the vocabulary in many AAC devices, which largely depict concepts or words that they already communicate through their body language (i.e. the mand function). Especially in Angelman syndrome, we see that vocabulary representing the "social interaction" function truly captures their motivation to communicate. They are not alone in this, but systemic barriers are high for AAC users to fully include in society (Blasko, 2025). When people who cannot speak, cannot start or initiate contact in an appropriate way, they often find other, less appropriate ways to seek or keep attention, or they shut down. Both can be, at least partially, prevented with proper AAC access and implementation.

**Discussion:** When we take together the lessons we've learned in our practice and the recent insights in AAC it shows us that we have to make a shift from "training" to "interaction" when it comes to AAC. We have to make it fun, meaningful and accessible. AAC is not a thing or goal in itself, it is how we interact with each other and how we interpret this interaction. This all comes back to the self-determination theory of Deci & Ryan (2012). We will conclude how AAC can aid autonomy, competence and connection between two or more individuals.

**Key words:** AAC, participation, meaningful interaction, communicative competence.

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## ID 71 ORAL PRESENTATION

### People with Profound Intellectual and Multiple Disabilities/Polyhandicap, Families, and Institutional Caregivers: The French EVAL-PLH Cohort. Results and Perspectives

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**Introduction:** Research on profound intellectual and multiple disabilities (PIMD)/polyhandicap remains scarce. Existing studies mainly rely on retrospective or cross-sectional data, which limits understanding of temporal changes. Longitudinal approaches, such as cohort studies, make it possible to analyze dynamic evolutions and interactions between factors. Established in 2015 (funded by DGOS-PREPS 2013 and INSERM-IRESP 2013), the French EVAL-PLH cohort was designed to fill this gap. This presentation aims (1) to describe the work conducted from the first two data collection waves and (2) to outline future developments.

**Methods:** The cohort investigates health status and care pathways of individuals with PIMD/polyhandicap, as well as the impact of this condition on family and professional caregivers. The first two follow-up periods (2015-2016 and 2020-2021) have been completed, and the third (2025-2026) is underway. The project involves public and private rehabilitation centers, medico-social facilities, and neuropediatric services.

**Results:** The first two waves included more than 1,000 individuals with PIMD, 600 family caregivers, and 600 professionals. Analyses provided an unprecedented body of knowledge, highlighting the diversity of clinical profiles, heterogeneity of care practices, and the heavy burden borne by caregivers. Building on this foundation and strong field partnerships, new projects have emerged to explore family experiences, professionals' quality of life, and home-based care, leading to the creation of the French PolyRENE research network.

**Conclusion:** The Eval-PLH cohort represents a unique framework for the long-term observation of people with PIMD/polyhandicap. It has improved understanding of care trajectories and caregivers' experiences, while strengthening a nationwide collaborative research dynamic.

**Key words:** profound intellectual and multiple disabilities, polyhandicap, cohort, research network



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# Understanding the Neurobiology

*-abstracts-*

## ID 1 POSTER PRESENTATION

### One of the Eight Known Cases Worldwide: A 7-Year-Old Girl with a De Novo RYBP Variant and Syndromic Neurodevelopmental Disorder

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**Introduction:** Pathogenic variants in RYBP (RING1 and YY1 Binding Protein), a component of the Polycomb Repressive Complex 1, were recently identified as a cause of syndromic neurodevelopmental disorder. To date, only seven patients have been reported worldwide, presenting with global developmental delay, hypotonia, and congenital anomalies.
Reported pathogenic variants include both copy-number variants (CNVs) and single-nucleotide variants (SNVs), the latter being particularly rare and—according to the literature so far confined to the N-terminal domain of RYBP. Our patient carries a distinct de novo SNV in RYBP (NM_012234.6:c.314G>C, p.Cys105Ser)—functionally similar to the variant c.132C>G (p.Cys44Trp) previously published by our co-author R. Płoski et al., 2025—expanding the mutational spectrum of SNVs in RYBP.

**Methods:** Trio-based whole exome sequencing (WES) was performed, followed by Sanger confirmation and segregation analysis, in a 7-year-old girl with global developmental delay, hypotonia, dysmorphic features, and congenital anomalies.

**Results:** We identified a heterozygous de novo RYBP variant, NM_012234.6:c.314G>C (p.Cys105Ser), absent in both parents. The phenotype overlaps with previously described RYBP-related cases. The variant is located within the N-terminal domain, consistent with the reported mutational cluster.

**Conclusions:** This case broadens the mutational and phenotypic spectrum associated with RYBP-related neurodevelopmental disorder and highlights the importance of reporting such rare cases to improve genotype – phenotype correlations.

**Key words:** RYBP; neurodevelopmental disorder; de novo variant; whole exome sequencing; genotype–phenotype correlation

## ID 2 POSTER PRESENTATION

### Molecular and Clinical Insights from Seven Patients with Crisponi Syndrome from Southeastern Turkey

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**Introduction:** The clinical phenotype is characterized by dysmorphic facial features including full cheeks, micrognathia, a high-arched narrow palate, low-set ears, and a depressed nasal bridge, dysregulated thermoregulation and paradoxical sweating, facial muscle contractions triggered by tactile or emotional stimuli during early infancy, skeletal abnormalities such as camptodactyly and scoliosis. The disease is frequently associated with high neonatal mortality; however, early recognition and symptomatic management can improve survival and clinical outcomes.

**Methods:** Seven patients from six unrelated families originating from southeastern Turkey were included in this study. Detailed clinical evaluations were performed, and demographic, phenotypic, and ophthalmologic data were systematically recorded. Targeted gene panel sequencing was conducted in all patients to elucidate the underlying genetic etiology. Sequence alignment and variant interpretation were performed according to current ACMG guidelines.

**Results:** The most frequent reason for referral was neonatal hypotonia, accompanied by congenital flexion contractures of the hands and elbows that were evident from birth. The mean age at diagnosis was 3.0 years (range: 3 months–10 years). All patients exhibited varying degrees of clenched hands and camptodactyly, and one individual presented with scoliosis. The most consistent craniofacial features were microretrognathia and chubby cheeks, which were particularly prominent during infancy. Feeding difficulties requiring orogastric tube support were observed in all patients. All individuals demonstrated reduced or absent sweating; however, none experienced seizures secondary to hyperthermia. Ophthalmologic evaluation revealed decreased corneal reflex in four patients, all of whom had chronic keratitis. Notably, a 7-month-old male presented with bilateral megalocornea and unilateral (left-sided) glaucoma. Molecular analysis identified three pathogenic variants in CRLF1: NM_004750.5:c.708_709delinsT (p.Pro238Argfs6), c.776C>A (p.Ser259*), and c.983dup (p.Ser328Argfs2). The recurrent c.708_709delinsT (p.Pro238Argfs6)* variant was detected in five patients from four unrelated families, suggesting a possible founder effect in this population.

**Discussion/ Conclusion:** Crisponi syndrome should be considered in infants presenting with **neonatal hypotonia** and **congenital joint contractures,** findings that may initially lead to evaluation in neurology or pediatric clinics. Recognition of the **characteristic facial features** and **feeding difficulties** can facilitate early diagnosis. The clustering of cases in southeastern Turkey likely reflects a **founder effect** in the context of **high consanguinity**, highlighting the need for regional awareness and genetic counseling.

**Keywords:** Developmental delay, hypotonia, joint contractures, *CRLF1*



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## ID 3 POSTER PRESENTATION

### From Clinical Phenotypes to Mechanisms: Linking Human and Mouse Studies in Dup15q Syndrome

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**Introduction:** Duplication 15q syndrome (Dup15q) is a rare and debilitating neurodevelopmental disorder characterized by intellectual disability, autism spectrum disorder, epilepsy, and motor and language impairments. Despite its clinical heterogeneity, the underlying molecular mechanisms remain poorly understood. To better define the clinical phenotype and bridge it to preclinical models, we first established a prospective Dutch cohort and then explored the mechanistic contributions of UBE3A and neighbouring genes in novel mouse models.

**Methods:** The clinical arm included 37 individuals (16 interstitial, 21 idic(15); 27 maternal, 2 paternal, 8 unknown parent-of-origin) with genetically confirmed Dup15q syndrome recruited between 2024–2025. Data were collected via standardized caregiver questionnaires (Dup15q survey, CarerQOL, CGI) and multidisciplinary assessments. To model the genetic complexity, we generated a novel Dp7 mouse line (*Dp-In7tubgcp5-Ube3a*) carrying a 3.5 Mb duplication encompassing all non-imprinted 15q11.2–13.1 genes but disrupting *Ube3a*. This strain was crossed with a Ube3a overexpression line (*Tg-Ube3a-FL-OE2*) to dissect the synergistic effects of Ube3a and non-imprinted gene dosage on behavior, cognition, and seizure susceptibility.

**Results:** Clinically, idic(15) cases showed more severe developmental and motor impairments than interstitial cases, supporting gene-dosage–related phenotypic variation. In parallel, molecular characterization of the Dp7 model confirmed a ~50% increase in expression of the non-imprinted genes, while behavioral testing revealed that increased dosage of these non-imprinted genes did not exacerbate Ube3a-driven phenotypes in the assays tested.

**Conclusions:** This combined clinical–translational study strengthens the link between human Dup15q phenotypic variability and underlying gene dosage effects. The prospective cohort establishes a foundation for natural history studies and trial readiness, while the novel Dp7 mouse provides a complementary platform to dissect the contribution of non-imprinted genes and UBE3A interactions, paving the way toward mechanism-based therapies.

**Key words:** Dup15q syndrome, neurodevelopmental disorder, cohort study, mouse model



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## ID 85 POSTER PRESENTATION

### UBE3A-neighbouring genes on chromosome 15q11.2-13.1 contribute to Angelman syndrome phenotype

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**Introduction:** The main driver of Angelman syndrome (AS) is the lack of expression of the maternally inherited UBE3A gene on chromosome 15q11.2-13.1. This has been recapitulated in several AS mouse models showing a robust phenotype with behavioral rescue after Ube3a reinstatement. However, 70% of patients carry a larger deletion involving neighboring non-imprinted genes and present with a more severe phenotype. The role and interaction between UBE3A deficiency and loss of non-imprinted genes remains unknown.

**Methods:** We generated a deletion on mouse chromosome 7 which affects all non-imprinted genes (*Atp10a-Tubgcp5*) in the human 15q1.2-13.1 locus using CRISPR/Cas9. The Del7 (*Del-7Tubgcp5-Atp10a*) strain has a functional *Ube3a* copy, allowing us to independently remove the *Ube3a* copy when crossing the Del7 strain with the AS (Ube3a-E113X) strain. After molecular validation, mice were tested in a standardized behavioral battery, cognitive and seizure susceptibility paradigms.

**Results:** Genomic qPCR indicated a 50% decrease in copy number of various targets in the affected region. mRNA expression of all the genes within the deleted locus showed an approximate 50% reduction compared to WT levels. While Del7-AS mice were indistinguishable from AS mice in various behavioural tasks associated with AS, they showed significant differences in cognition and seizure susceptibility paradigms.

**Conclusions:** The novel Del7 mouse provides a powerful tool to study the impact of non-imprinted genes on the AS pathophysiology in combination with loss of UBE3A. Further testing using UBE3A-sensitive behavioural assays will confirm the face validity of this novel mouse model and potential for therapeutic endeavours.

**Key words:** Angelman syndrome, neurodevelopmental disorder, mouse model



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## ID 4 POSTER PRESENTATION

### DUP15q syndrome : Clinical and genetic description of a Spanish cohort

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**Introduction**: The chromosome region 15q11q13 is prone to genomic rearrangements, due to the presence of repeated DNA elements. Clinical phenotype variability of patients with 15q 11q13 duplication has been characterized and includes neurodevelopmental delay (NDD), autism spectrum disorder (ASD), language troubles, clumsiness and behaviour issues. The phenotype-genotype correlations point to link clinical severity to the parental origin of the duplication as well as the presence or absence of the Prader-Willi/Angelman critical region in the duplicated region. We present the clinical and molecular findings in 10 patients with duplications of 15q11.2-q13 followed up in our area.

**Methods:** aCGH of 180k (Oxford Gene Technology, OGT). Methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA, ME028, MRC-Holland), to assess the parental origin eight microsatellite markers were used; five were intern D15S11, D15S128, D15S113, D15S97, GABRB3 and three externs D15S194, D15S123, D15S13.

**Results**: A sample of 13 children are described, including clinical phenotype (ASD and behaviour troubles). There were 2 pairs of siblings (4 patients), their respective mothers were carriers. Although neurodevelopment delay was present in the first year of live, and more evident at the age of 2 with constant language delay, some patients were not diagnosed until the adulthood, when behaviour troubles became more important.

**Conclusions:** Dup15q is a rare disorder and one of the recognized causes of ASD and NDD, easy to rule out using molecular technics as aCGH and MLPA. It is crucial to study the progenitors of patients with Dup15q syndrome, to identify possible carriers and provide genetic counselling for future offspring. Inheritance of the duplication or tetrasomy may influence clinical phenotype of Dup15q patients.

**Key words**: Dup15q, autism spectrum disorder (ASD), neurodevelopmental disorder (NDD), Language delay.

## ID 5 POSTER PRESENTATION

### Decoding CAMK2A: Deep Phenotyping of a Unique Cohort Sheds Light on a Crucial Learning and Memory Pathway

Anjuli Dijkmans[1], Margreth van der Lugt[1], Renate Gericke[2], Leontine ten Hoopen[3], Pieter de Nijs[3], Cindy Navis[4], Laurentine Kamminga[5], Mandy van Drunen[5], Koen Dekkers[5], Joshua Cheung[6], Lianne Vogel[6], Renee Gouw[6], Charlotte de Konink[7], Margaret Stratton[8], Howard Schulman[9], Rianne Oostenbrink[1], Marie-Claire de Wit[10], Tjitske Kleefstra[11], Geeske van Woerden[12], Danielle Veenma[1]

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**Introduction**: CAMK2 proteins are central to synaptic plasticity and represent a key molecular pathway for learning and memory. Pathogenic variants in one of the four CAMK2 genes (CAMK2A, B, G, and D) are linked to neurodevelopmental disorders, yet natural history data remain sparse.

**Methods**: We present findings from a prospective cohort study of **42 individuals** with pathogenic CAMK2A variants. A multidisciplinary team performed in-depth phenotyping using questionnaires, medical records, and neuropsychological interviews. Variant pathogenicity was assessed using the PRiSM assay.

**Results**: Findings reveal a strikingly consistent phenotype: global developmental delay or intellectual disability (100%), speech-language delay (100%), and motor delay (76%). Neurobehavioral features were highly prevalent, including attention deficits (93%), emotion regulation difficulties (81%), and sensory sensitivities (78%). Additional comorbidities included epilepsy (29%), gastrointestinal dysmotility (50%), and sleep disturbances (55%).
Individuals carrying variants in the regulatory domain exhibited more severe phenotypes than those with variants in the kinase domain, including higher rates of profound ID (80% vs. 33%), non-verbal status (91% vs. 25%), sleep problems (91% vs. 63%), and impaired ambulation (64% vs. 13%).

**Discussion**: This study establishes CAMK2A as a pure neurodevelopmental condition affecting all developmental domains. This study underscores the urgent need for cross-gene comparisons to better understand the full clinical spectrum and therapeutic avenues.



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## ID 7 POSTER PRESENTATION

### Familial Chromosomal Translocation Reveals Novel Brain-Specific Transcripts Associated with Mild Cerebellar Ataxia

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Balanced chromosomal rearrangements, occurring in approximately 1 in 500 live births and in 1 in 30 individuals with neurodevelopmental disorders (NDD), offer a unique opportunity to investigate genomic regions surrounding breakpoints and identify novel disease-associated genes and mechanisms.

We report a detailed breakpoint analysis of a familial translocation between chromosomes 8 and 20, segregating with a mild cerebellar ataxia phenotype across five generations, affecting 13 carriers.

The chromosome 8 breakpoint disrupts a previously uncharacterized chimeric transcript formed by cis-splicing of adjacent genes *PURG* and *TEX15*. This PURG-TEX15 transcript is expressed in testis and the adult human brain—specifically in the cerebellum, substantia nigra, and amygdala—but not in fetal brain tissue. We demonstrated that it gives rise to a stable protein product, which may be functional. While *PURG* belongs to the purine-binding protein family, its specific role remains elusive. Notably, its homolog *PURA* has been implicated in a neurodevelopmental syndrome, highlighting the relevance of PUR-family genes in brain function.

The chromosome 20 breakpoint truncates a brain-specific isoform of *DLGAP4*, a key component of the postsynaptic density protein complex, implicated to have a role in neurogenesis and neuronal migration. *DLGAP4* interacts with *SHANK1* and *PSD95*, and we show that these proteins co-localize at the synapse and are co-regulated. Mouse model of *DLGAP4* exhibit tremor and autism-like behaviors and cognitive disorder.

The translocation leads to another chimeric transcript bringing the PURG and the DLGAP4 genes together. We have shown that the predicted chimeric PURGaltDLGAP4 transcript has the capacity to make a protein product. This might replace PURG-TEX15 protein in the brain of the patients where it was expressed. Molecular dynamics simulations of PURG variant proteins indicated that the dimerization interface of PURG homo- and heterodimers involving the PURGaltDLGAP4 variant are notably less stable than that of wild-type homo-and heterodimers.

These breakpoints induce disruption that affect chromatin architecture and truncate two brain-specific transcripts—*PURG-TEX15* and *DLGAP4*—both of which are strong candidates for contributing independently or synergistically to the mild ataxia phenotype observed in this family.

**Key words:** DLGAP4, PURG, PURG-TEX15, cerebellar ataxia, balanced chromosome translocation, t(8 ;20), cis-SAGE, chimeric transcript.



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## ID 8 POSTER PRESENTATION

### Integrative Genomic Approaches Reveal Novel Etiologies in Cerebral Palsy and Related Neurodevelopmental Phenotypes

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**Background:** Cerebral palsy (CP) is a clinically and genetically heterogeneous neurodevelopmental disorder by permanent, non-progressive motor deficits. While prenatal and perinatal risk factors, such as prematurity or hypoxic injury, are often implicated, an increasing number of studies suggest that genomic testing has increasingly revealed monogenic contributions to its etiology. To improve diagnostic precision and better characterize the underlying molecular mechanisms, we evaluated a Turkish multicenter cohort of individuals with CP and CP-like phenotypes through integrated genomic approaches.

A total of 66 previously unsolved cases clinically diagnosed with CP or CP-like phenotypes underwent comprehensive genomic analysis using exome/genome sequencing data, with an in-house genome analysis pipeline supported by detailed clinical re-evaluation. Pathogenic or likely pathogenic variants were identified in **36.4% (24/66)** of cases, while **25.8% (17/66)** harbored variants of uncertain significance (VUS) in genes associated with neurodevelopmental disorders. We detected most of our variants in frequently reported CP genes, including *SPAST, KIF1A, PLA2G6, CTNNB1, L1CAM,* and *SYNGAP1,* underscoring the genetic and phenotypic diversity of CP.

To further strengthen variant interpretation in select cases, transcriptomic validation was performed. In one individual presenting with CP-like motor impairment and developmental epileptic encephalopathy, a novel splice-affecting variant in the *CHKA* gene was confirmed as disease-causing through trio whole-genome sequencing combined with RNA sequencing, demonstrating the clinical value of incorporating functional studies in genomic diagnostics.

Our results emphasize the complex genetic basis of CP and highlight the value of genomic analysis and integrated multi-omics approaches for enhancing diagnosis in neurodevelopmental disorders. This study is the first to characterize the CP genome in Türkiye and underscores the importance of expanding access to genomic testing for underrepresented populations.

**Keywords:** Cerebral palsy, Genetic diagnosis, Next-generation sequencing

**Grant:** This study was primarily funded by the Scientific and Technological Research Council of Turkey (TÜBİTAK, Project No: 221S889, *Deep-CP*) and supported by the RareBoost Project (EU Horizon 2020, Grant No: 952346).

## ID 10 POSTER PRESENTATION

### A truncating variant in ADORA3 encoding Adenosine Receptor A3, is associated with autosomal dominant Tourette Syndrome.

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**Introduction**: Gilles de la Tourette syndrome (TS) represents a heterogeneous childhood-onset psychiatric disorder characterized by persistent motor and vocal tics, associated with abnormal development of brain networks involved in sensory and motor processing. with an estimated prevalence of 1% in children and adolescents. Comorbidity with other disorders, including attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), and autism spectrum disorder (ASD) points to a common etiological thread along an impulsivity-compulsivity continuum. Copy number variations, genome-wide association studies and next generation sequencing have implicated variants in histidine decarboxylase, *SLITRK1,* dopamine and serotonin receptor genes ,in the development of TS. Recently an autosomal dominant form of TS has been associated to Gamma-Aminobutyric Acid Type B Receptor *GABBR1* in one family.

**Methods and Results**: We report a family with autosomal dominant TS affecting the father and paternal grandmother, of an adolescent male proband presenting TS, obsessive compulsive disorder, ADHD and moderate intellectual disability (ID). WES trio sequencing followed by segregation analysis in the affected family members (proband, father and paternal grand mother) identified a rare truncating variant in *ADORA3* (1p13.2) NM_000677.3c.395delG; p.Gly132fs*11 co-segregating with the disease.

**Conclusions:** In the central nervous system (CNS), the four subtypes of adenosine receptors (A1, A2a, A2b and A3) acts as a neuromodulators of serotonine and other neurotrasmitters. A3 receptors acts trough inhibition of adenylyl cyclase (AC) and phospholipase, playing a protective role in brain ischemia and excitotoxicity and have been implicated in neuroimmunomodulation, psychostimulant addiction and mood regulation through circadian clock and sleep homeostasis. This finding suggests a possible role of the adenosergic system in the pathogenesis of TS. Further studies, the identification of more families and functional studies to confirm the pathogenicity of the identified variants, are necessary. The application of new technologies like epigenetics and proteomics and the development of selective modulators of adenosine receptors will pave ways to new treatments for TS and related neuropsychiatric disorders.

**Key words**: Tourette Symdrome (TS) ; Adenosine Receptor type A3 (ADORA3) ; obsessive-compulsive disorder (OCD); attention deficit hyperactivity disorder (ADHD)

## ID 13 POSTER PRESENTATION

### Integrating Radiogenomics into Neurogenetic Diagnostics

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**Introduction:** Neurogenetic disorders present a diagnostic challenge due to overlapping clinical and radiologic features. *Forward phenotyping*—formulating of a preliminary radiology-based diagnosis before molecular confirmation—offers a strategy to accelerate recognition and improve diagnostic precision. This study evaluates the diagnostic contribution of forward phenotyping across neurogenetic subgroups using an integrated radiogenomics approach.

**Methods:** This retrospective study was conducted by the Ankara University Radiogenomics Study Group. The cohort comprised 93 patients with genetically confirmed neurogenetic diagnoses selected from the Radiogenomics Database, which systematically integrates genomic and neuroimaging data.
Prior to molecular confirmation, all patients underwent detailed MRI assessment, during which blinded neuroradiologists recorded forward phenotypic impressions based solely on imaging and limited clinical data (e.g., developmental delay, microcephaly, seizures). After genomic results were available (targeted panels or exome sequencing), these preliminary assessments were compared with molecular diagnoses to determine accuracy and subgroup-specific diagnostic yields. Following confirmation, reverse phenotyping was performed to enrich the database for future learning, enabling continuous feedback to neuroradiologists and supporting AI-based radiogenomic model development.

**Results:** Forward phenotyping contributed to early and accurate recognition in 32 of 93 patients (34%).
Within the mitochondrial disease subgroup (13 patients; 14% of the cohort), 9 underwent forward phenotyping and 7 of these (7/13; 53.8%) received correct preliminary diagnoses later confirmed by genetic testing. Correctly predicted cases included MELAS, ECHS1-related Leigh-like disorder, mitochondrial DNA depletion syndrome (hepatocerebral type), nuclear-encoded complex I deficiency type 21, and complex IV deficiencies types 1 and 2.
Two mitochondrial cases were misclassified (one as a metabolic disorder, later identified as Combined Oxidative Phosphorylation Deficiency 23; another as a urea cycle disorder, later confirmed as Mitochondrial Complex V deficiency, nuclear type 1).
In the metabolic subgroup (17 patients; 18% of the cohort), forward phenotyping was applied to 8, with 7 (41.2%) correctly identified. Leukodystrophies and cortical malformations showed lower predictive accuracy (<30%). MRI features most predictive of mitochondrial disease included bilateral basal ganglia and periventricular hyperintensities, stroke-like cortical lesions, and diffuse cerebellar atrophy, enabling effective early recognition before molecular confirmation.

**Conclusion:** Forward phenotyping through structured neuroimaging analysis facilitated early and reliable recognition in one-third of neurogenetic cases, achieving the highest diagnostic yield in mitochondrial diseases (7/13; 53.8%). Beyond establishing radiologic–disease correlations, this study demonstrates the feasibility of gene-radiophenotype integration and highlights the value of continuous radiogenomic feedback for developing AI-assisted diagnostic tools. Despite limitations in sample size and single-center design, our findings underscore the growing potential of radiology-driven precision medicine in neurogenetic diagnostics.

**Key words**: Radiogenomics, Neurogenetics, Forward phenotyping, MRI



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## ID 14 POSTER PRESENTATION

### Expanding the evaluation of skeletal anomalies in patients with KBG syndrome ; recommendations for clinical practice

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**Introduction:** KBG syndrome is a rare autosomal dominant neurodevelopmental disorder caused by ANKRD11 haploinsufficiency and is characterized by short stature, distinctive facial features, intellectual disability or developmental delay, congenital anomalies and skeletal anomalies. Although skeletal anomalies are reported in about 75% of cases, their nature and extent in relation to growth are largely unknown. Therefore, this study aims to asses the prevalence of skeletal anomalies in KBG syndrome and explore if there is a relation with short stature.

**Methods:** This retrospective cohort study included patients with a confirmed diagnosis of KBG syndrome, with available radiographic images at the Radboud University Medical Centre. The radiographs were re-evaluated by a radiologist focusing on the presence of spinal, costal, vertebral and hand anomalies using standardized radiological criteria.

**Results:** In our cohort of 38 persons with KBGS, 92% shows skeletal anomalies on radiographic imaging. The most frequent observations on the radiographs were spinal anomalies (74%) and costal anomalies (40%). Specifically, lordosis (36%) and abnormal skeletal age (31%) had the highest prevalence. Patients with short stature (n = 14) showed higher prevalences of kyphosis and delayed skeletal age.

**Conclusion:** This study demonstrated a high prevalence of skeletal anomalies with a broad variety in individuals with KBGS.

**Key words:** KBG syndrome, KBGS, skeletal anomalies, short stature, scoliosis



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## ID 15 POSTER PRESENTATION

### Novel microdeletion syndrome identified on chromosome 7?

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Here, we report on a 2-year-old girl born 37+1 with growth retardation (IUGR/SGA), primary microcephaly, developmental delay and the following facial dysmorphisms: round cheeks, broad nasal tip, epicanthus.

We performed whole exome sequencing including parental DNA samples with subsequent trio analysis as well as exome wide gene dosage (CNV) analysis. Target enrichment was performed using Twist Exome with custom specific probes and subsequent sequencing using NovaSeq 6000, Illumina.

Through CNV analysis we identified a heterozygous *de novo* 4,7 Mb deletion on the long arm of chromosome 7 (seq[GRCh38] del(7)(q35q36.1)) that affects 94 genes, including EZH2 and KCNH2. To our knowledge, no known microdeletion syndrome is described for this region and no comparable deletion has been reported in literature or databases so far. The heterozygous deletion of the currently disease-associated genes cannot completely explain the patient's phenotype. In contrast to the growth restriction seen in our patient, the deleted gene EZH2 is associated with Weaver syndrome, an overgrowth syndrome. No other relevant SNV or CNV could be identified in the trio analysis. Thus, we suggest a not yet described contiguous gene syndrome to be the underlying cause of the symptoms seen in our patient. Additionally, the deletion includes the gene KCNH2 and the patient is therefore at risk for long QT syndrome.

This case report illustrates that gross deletions can be identified through whole exome sequencing and that those copy number variations bear the risk of identifying incidential findings. Furthermore, we might have identified a novel, not yet described contiguous gene syndrome on the long arm of chromosome 7 presenting with developmental delay, growth retardation, microcephaly and facial dysmorphisms.

**Key words:** growth retardation, EZH2 haploinsufficiency, contiguous gene syndrome, incidential finding

## ID 16 POSTER PRESENTATION

### Is the Autism Phenotype in Phelan-McDermid Syndrome (PHMDS) more Friendly?

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**Introduction:** The PHMDS phenotype is characterized by an increased prevalence of autism and intellectual disability (ID). Autism in individuals with moderate or severe ID is commonly associated with challenging behaviour.

**Method:** All known individuals with PHMDS in Norway are invited to participate in this ongoing study. We have conducted structured interviews of family members/ caregivers and administered validated questionnaires. The 'Social Communication Questionnaire' (SCQ) is used to screen for autism symptoms. The 'Developmental Behavior Checklist' (DBC) is used to assess behavioural and emotional symptoms.

**Results:** Currently 32 (17 males) individuals have been included. Mean age is 20.7 years (SD =12.3)
Mean SCQ is 17.3 (SD = 6.4). The autism domains of 'social interaction' and 'language and communication' tend to be rated higher than scores on 'restricted, repetitive, and stereotyped behaviours'. Only a few individuals scored positively on items on the DBC measuring typical repetitive autism symptoms or challenging behaviour.

**Discussion:** The scores on SCQ and DBC seem to correspond to the descriptions done by parents who were asked about the strengths of their family member with PHMDS. They commonly used words such as 'friendly', 'sociable', 'happy' and 'loving'.

**Conclusion:** Despite clinical important autism challenges in social and communication domains, the autism phenotype in PHMDS appears to be characterized by a friendly appearance. Challenging and self-injurious behaviour were rarely seen in our population with PHMDS.

**Key words:** Phelan-McDermid syndrome. Autism, SHANK3, 22q13.3 deletion syndrome



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## ID 17 POSTER PRESENTATION

### Whole Exome Sequencing in a Tunisian cohort of 100 children with Neurodevelopemental Disorder

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**Introduction:** With a prevalence of around 5–10%, Neurodevelopmental disorders (NDD) are defined as conditions impairing the growth and development of the brain and/or central nervous system leading to delays in acquisition of skills during human development. The disorders are highly heterogeneous and multifactorial, affecting various developmental areas including social, cognition, language, and motor development domains. Since the implementation of high throughput genetic techniques in the investigation of patients with NDD, the prevalence of pathogenic genetic variants are estimated to reach 40%.
Whole Exome Sequencing (WES) has recently been implemented in the diagnostic workflow of Tunisian patients with highly presumed genetic conditions.
We report on the clinical and genetic results of the first large Tunisian pediatric cohort of NDD investigated with WES.

**Methods:** Family history and clinical data were collected from a monocentric pediatric cohort referred to the Department of Genetics at Mongi Slim Hospital (Tunis, Tunisia) for NDD. The genetic study included a conventional karyotype in a first-tier.
Whole Exome Sequencing was performed in Solo on peripheral blood lymphocytic DNA using sequencing by synthesis (Illumina technology) and targetting approximately 99.3% of the RefSeq protein coding region. Variant interpretation was performed using an in-house software to prioritize variants based on the guideline recommended by the American College of Medical Genetics and Genomics (ACMG).

**Results:** A cohort of 100 children with NDD was included in the study. Psychomotor delay was the most common feature, reported in 72 patients. Intellectual disability was diagnosed in 44 cases, microcephaly in 32 cases, and language delay in 30 patients. Epilepsy was diagnosed in 23 cases.
Autism spectrum disorder or stereotypic behaviour was reported in 13 cases. Behavioral concerns were present in 12 patients. The NDD was associated with dysmorphic features in 54 cases, and with congenital heart defects in 8 cases.
The conventional karyotype was normal in all the cases. WES identified a pathogenic or probably pathogenic variant in 43 cases and a variant of uncertain significance (VUS) in 21 cases. Among the latter group, segregation study and phenotypic assessment allowed the reclassification of 2 VUS as probably pathogenic, respectively in *THOC6* and *ATP6V0A2* genes. Among the clinically relevant variants, a single nucleotide variant (SNV) was identified in 35 patients and a copy number variation (CNV) in 8 patients.

**Discussion/conclusion:** In the reported series, the overall diagnostic yield of WES in NDDs is approximately 36%, with varying rates between 31% for isolated NDDs and 53% for NDDs accompanied by additional conditions.
In our study, WES allowed a diagnostic yield of 45%, a rate that is in line with the literature.
WES provides a valuable tool of increasing clinical utility to investigate NDD that not only provides relief after arduous diagnostic odysseys but also avoids further diagnostic investigations. The diagnostic utility increases especially in patients with severe and/or multisystemic conditions. The molecular confirmation enables informed patient management, and facilitates accurate genetic counseling and risk assessments, along with providing families with prenatal options.

**Key words:** neurodevelopmental disorder, intellectual disability, psychomotor delay, Whole Exome Sequencing, single nucleotide variant, copy number variation, genetic counselling

## ID 18 POSTER PRESENTATION

### A Systematic Review Illustrates the Expanding Clinical and Molecular Landscape of Helsmoortel-Van der Aa syndrome

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**Background**: Helsmoortel-Van der Aa syndrome (HVDAS) is a rare multisystemic neurodevelopmental disorder caused by pathogenic variants in the Activity-Dependent Neuroprotective Homeobox Protein (ADNP) gene. Since the extensive clinical description of a cohort of 78 affected individuals in 2019, numerous reports described additional cases affected by the condition. However, no systematic synthesis of the clinical and molecular spectrum of these additional individuals has been conducted to date.

**Methods**: In accordance with the PRISMA 2020 guidelines, we performed a systematic review of all published reports describing individuals with genetically confirmed HVDAS. Clinical characteristics, comorbidities, and developmental milestones were systematically extracted and compared with previously established reported features to identify novel or underrecognized manifestations.

**Results**: A total of 105 individuals reported across 34 publications were included. Of these, 66 were clinically and genetically evaluated, and 39 were only analyzed genetically. Our analysis refines the phenotypic spectrum of HVDAS, including developmental delay, autism spectrum disorder, dysmorphic facial features, and congenital heart defects. We highlight as-yet-unnoticed manifestations including oromandibular anomalies, hormonal irregularities and prenatal presentation. The additional literature also allows us to characterize in more detail the ophthalmological abnormalities, gait disturbances, and the cognitive profile of HVDAS. Advances in ADNP methylation profiling further enhance diagnostic precision and variant interpretation in this evolving neurodevelopmental syndrome.

**Conclusions**: This systematic review provides a comprehensive synthesis of the clinical, genetic, and epigenetic landscape of HVDAS. The expanding phenotypic heterogeneity emphasizes its multisystemic nature and supports the need for multidisciplinary management.

**Key words:** Helsmoortel-Van der Aa syndrome; HVDAS; ADNP; autism; neurodevelopmental dis-order; systematic review



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## ID 19 POSTER PRESENTATION

### Severe epilepsy, prominent myoclonus and dystonia in patient with AGO1 p.Phe180del de novo variant (Case Report)

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**Objectives:** Neurodevelopmental disorder with language delay and behavioral abnormalities, with or without seizures associated with the *AGO1 de novo* variants, is a rare disorder with evolving phenotypic characteristics. Here, we present a new patient with p.Phe180del de novo heterozygous variant in the *AGO1* gene. Aside from global developmental delay, the most prominent neurological symptoms, were pharmacoresistant seizures, tremor, dystonia and myoclonus.

**Methods:** Standard karyotyping, array-CGH and trio-exome analysis were performed on the patient and his parents. Methylation array analysis was indicated, but results are not yet available. We conducted a retrospective phenotypic analysis. Informed consent was obtained from the parents.

**Results:** Genetic testing was indicated at the age of 11 years. Following normal results from the array analysis, trio exome analysis was performed, identifying a de novo AGO1 p.Phe180del variant. An additional genetic finding was a hemizygous variant in a novel candidate gene for autism, *FAM120C*(NM_017848.6):c.176G>T (p.Gly59Val), which was inherited from a healthy mother.
The male patient was born in 2010 as the result of the fourth pregnancy, which was at imminent risk of miscarriage in the 29^(th) week of gestation. He was born at term with a normal perinatal period. There is a history of intellectual disability in the father's family.
The boy's first symptom was hypotonia, which appeared at nine months of age. This was followed by a global developmental delay: he only began walking independently after the age of two, and he also experienced speech and social delay, as well as intellectual disability. He also presented with short stature, facial dysmorfism, failure to thrive, hypotonia, hemiparesis, hemiplegia, tremor, and nocturnal enuresis. He has myopia and strabismus. A MRI scan of his brain at the age of seven revealed small demyelinating lesions in the frontal subcortical white matter. Metabolic studies, including CSF analysis, were normal.
The patient's most prominent health difficulty was epilepsy. It started at the age of five years as absence seizures, which were controlled by antiseizure medication (ASM). After the age of seven, he developed variable seizures 1. focal motor seizures with impaired consciousness, with twitching of the limbs with alternation of sides, occasionally perioral automatisms, 2. focal motor seizures without disturbance of consciousness, 3. seizures of the character of atypical absences (non-motor generalised seizures) with EEG findings evolving to epileptic encephalopathy. Overall, due to pharmacoresistance, 12 ASM regimens were prescribed over eight years, including seven different three-drug combinations and two different four-drug combinations. He is currently seizure-free on a combination of valproic acid, levetiracetam, rufinamide, perampanel and zonisamide.

**Conclusion:** We present a new case report of AGO1 neurodevelopmental disorder associated with variable, severe seizures that were difficult to control with ASM, as well as extrapyramidal symptoms. Further studies are required to understand the impact of FAM120C, a novel candidate ASD gene.

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## ID 20 POSTER PRESENTATION

### Neurodevelopmental phenotype caused by complex structural chromosomal rearrangement – small cohort of patients with 8p inverted duplication/deletion syndrome

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**Introduction:** 8p inverted duplication/deletion syndrome is rare complex structural chromosomal rearrangement with a wide range of clinical manifestations - psychomotor and language delay, hypotonia and dysmorphic facial features. It's compound of deletion and duplication of inverted part of short arm of the 8 chromosome. The main mechanism is ectopic recombination due to presence of clasters of olfactory receptor and defensin genes in region 8p23.1 containing low-copy repeats regions (LCR). There is no evidence of the corellation beetwen duplication size and more severe course.

**Methods:** We collected and analyzed clinical data (family history, pre- and postnatal information concerning congenital anomalies and development, dysmorphology examination, photos) and cytogenetics data (kariotyping and array comparative genomic hybrydysation were done). Also parents were tested for the same aberrations.

**Results:** We present 5 patients with 8p inverted duplication/deletion syndrome under the care of our outpatient clinic (4 were diagnosed in our department, 1 of them was previously diagnosed). All patients have developmental delay or/and intellectual disability, certain present known dysmorphic features. The deletion size varies from 1,7 to 7,89 Mb, duplication size varies from 3,68Mb to 28,49Mb. Probably in all patients rearrangement occured by non-allelic homologous recombination, only one case is familial.

**Key words:** 8p, 8p inverted duplication/deletion syndrome, low copy repeats, genomic rearrangement

## ID 23 POSTER PRESENTATION

### Neurodevelopmental disorders and genotype-phenotype correlation in Smith Magenis Syndrome: systematic review and French cohort results

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**Introduction:** Smith Magenis Syndrome is either due to a deletion in 17p11.2 locus or to a pathogenic variant in *RAI1* gene and is associated with neurodevelopmental disorders (NDDs). We present the results of a systematic review assessing prevalences of autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), intellectual disability disorder (IDD) and specific learning disabilities in Smith Magenis Syndrome, alongside results of phenotype-genotype correlations assessed in the French cohort.

**Methods & Results:** Firstly, a systematic review assessing prevalences of NDDs was performed. 1941 articles were identified and 14 were included in this review for a total of 451 patients. 6 studies (n=220 patients) assessed ASD, with pooled prevalences of 43% and 80% for deletion and *RAI1* samples respectively. 6 studies assessed ADHD (n= 174 patients). Only one study used standardized clinical criteria, reporting 100% prevalence. Other studies assessed impulsivity, hyperactivity, attention deficit with pooled prevalences of 78%, 76% and 96% respectively. 9 studies reported IDD, ranging from 67% to 100%. For deletion carriers, pooled prevalence was 93%, mostly moderate (43%), while 80% was reported for *RAI1* carriers, mostly mild (69%). Specific learning disabilities were described for 9% of deletion 17p11.2 patients. Secondly, French cohort of 53 people presenting with Smith Magenis syndrome and evaluated in a specialized rare diseases center for challenging behaviors (GénoPsy) is presented in regards of NDDs phenotype-genotype correlations. Findings in regards of ADHD and ASD are highly consistent with results of the systematic review: A formal ASD diagnosis was documented in 46.5% of deletions carriers versus 77.8% of *RAI1* cases, a difference that did not reach statistical significance (p = 0.143). ADHD was highly prevalent in the cohort, affecting 76.7% of patients with 17p11.2 deletions and 88.9% of those with *RAI1* variants. Inattention was nearly universal (81.4% vs. 100. Prevalence of IDD reached 86.0% (37/43) of patients with 17p11.2 deletions. In contrast, none of the patients carrying a pathogenic *RAI1* variant had documented IDD (0/9), a highly significant difference for overall ID ($p = 1.3\times10^{-6}$).

**Conclusion**Systematic review and French cohort results highlight a marked divergence in neurodevelopmental expression according to genotype in Smith Magenis syndrome: while ADHD is identified as an overall core symptom, ASD tends to be more frequently associated with *RAI1* variants and IDD with 17p11.2 deletions. There is a critical need to systematically and precisely assess NDDs in Smith Magenis syndrome to better address behavioral outcomes.

**Keywords:** Smith magenis syndrome, phenotype-genotype correlation, neurodevelopmental disorders

## ID 25 POSTER PRESENTATION

### MED13L syndrome : Contribution of the GENIDA database to patient phenotyping

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**Background:** MED13L pathogenic variations cause the so-called MED13L-syndrome. The condition is characterized by a developmental delay in both motor and language acquisition, leading to a mild to severe intellectual disability (ID). A majority of patients may also exhibit malformations, particularly in the cardiac or skeletal system. GenIDA international project aims to improve the knowledge and management of rare genetic diseases.

**Methods:** The present study uses standardized HPO terms to comprehensively phenotype individuals' descriptions extracted from the literature and to compare patient phenotypic data from the GenIDA database. Additionally, by comparing variant identified in patients reported in the literature, we aim to identify potential phenotype-genotype correlation.

**Results:** There was no significant difference in the phenotype description between individuals from the GenIDA cohort and individuals from the literature. Nevertheless, the results highlight that developmental delay, dysmorphic features, and cardiac defects are predominantly described in the cohort based on scientific reports, whereas sensory defects, walking difficulties, and limb malformations are more emphasized in reports from families.
Further analysis comparing patients with missense variants to those with loss-of-function variants revealed statistically significant differences in four criteria : absence of speech, lack of independent walking, epilepsy, and cardiopathy were more prevalent in individuals with missense variations.

**Conclusion:** This study highlights the value of data reported by families in describing the complete phenotype of rare genetic syndromes. Patients with missense variants presented statistically more pronounced neurological symptoms than those with loss-of-function variants.

**Key words:** MED13L syndrome, Intellectual disability, Genida project

## ID 26 POSTER PRESENTATION

### Multilevel approach to unravel neuropathogenic mechanisms of SIN3A haploinsufficiency in Witteveen-Kolk Syndrome

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Neurodevelopmental disorders (NDDs) are a heterogeneous group of syndromes that typically manifest early in development. NDDs are frequently characterized by *i*ntellectual disability/developmental delay (ID/DD) and resulting cognitive deficits. In our studies, we focus on Witteveen-Kolk Syndrome (WitKoS) characterized by mild ID, growth and feeding difficulties, autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). This syndrome is caused by heterozygous loss-of-function mutations in SIN3A, a gene that encodes for a transcriptional repressor and MeCP2 interactor. Preliminary studies performed in vivo showed that functional knockdown of Sin3a leads to reduced cortical neurogenesis and aberrant cortico-cortical projections in the developing mouse brain, as well as altered progenitor proliferation in the prefrontal cortex; however, little is known about the human-specific roles in cortical maturation. While much evidence suggests that defects in cortical development, particularly in cortical excitatory neurons, are one of the major reasons leading to the emergence of the phenotype, it is reasonable to assume that brain-wide changes further contribute to the manifestation of WitKoS, since proper functioning of the brain is highly dependent on the connectivity of different systems and regions. Importantly, the developing cortex is highly sensitive to its neurochemical environment, where either deficient or excessive levels of monoaminergic neuromodulators – dopamine, serotonin, and noradrenaline, all of which act over relatively long-time scales - will impair cortical development and function. To shed light on the pathogenic molecular mechanisms, we generated dorsal forebrain and midbrain organoids from patient-derived iPSCs and characterized them in parallel with (isogenic) control organoids. Data suggest that patient-derived dorsal forebrain organoids present a smaller size and an aberrant cytoarchitecture when compared to controls. A better understanding of the underlying biological mechanisms will open doors to investigate the possibility of therapeutic interventions and subsequent improvement of care.

**Key words;** Sin3a, neurodevelopment, neuromodulators, functional connectivity, in utero electroporation, neural organoids



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## ID 27 POSTER PRESENTATION

### X-linked disorders associated with RAB39B: a phenotype similar to FMR1-related disorders?

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Pathogenic variations in the RAB39B gene (X chromosome) cause intellectual developmental disorder (IDD; OMIM #300774) and/or early-onset Parkinson's disease (Waisman syndrome; OMIM #311510) in men. Two brothers, one of whom has IDD and Parkinson's symptoms, are presented along with their diagnostic journey. Their family history includes an uncle and two maternal great-uncles with IDD and Parkinson's disease for the uncle, as well as a sister with premature ovarian failure (POF). After a normal early childhood, learning difficulties led them to attend a special school and work in a protected environment. They experienced febrile tonic-clonic seizures at around 18 months of age and macrocephaly (+3 SD). They live independently.

The initial genetic analyses (2010-2011) — karyotype, ARX and FMR1 (21 repeats) studies — were normal. In 2023, trio exome sequencing (mother and two brothers) revealed a variant of unknown significance in NBEA that did not match family segregation. In 2024, trio genome sequencing (brothers and a healthy nephew) did not allow for a conclusion to be reached. But in 2025, RNAseq analysis showed a total loss of expression of RAB39B, a key gene in synaptic trafficking, neuronal autophagy, and dopaminergic neuron survival. Its loss of function activates the PI3K-AKT-mTOR pathway, causing macrocephaly, IDD, and early-onset Parkinsonism (under 45 years of age) sensitive to levodopa. A genome-oriented reinterpretation identified a deletion of the 3'UTR portion of exon 2 of RAB39B, probably due to the insertion of a mobile element, which explains the difficulty of detection by genome sequencing.

This study highlights the contribution of RNAseq in detecting abnormalities not identified by conventional methods. It reveals a phenotypic continuity between this X-linked IDD and Waisman syndrome, both of which are linked to a loss of RAB39B function. This syndrome, which mainly affects boys, has similarities with FMR1-associated disorders, with variable ID, macrocephaly, and risk of early-onset Parkinsonism. Neurological monitoring is essential, particularly for levodopa sensitivity.



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## ID 28 POSTER PRESENTATION

### Widening the IHPRF1's clinical and molecular spectrum through NALCN in silico structural analysis

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**Introduction**: Infantile hypotonia with psychomotor retardation and characteristic facies-1 (IHPRF1, OMIM#615419) is a rare, birth onset, autosomal recessive (AR) disorder caused by homozygous or compound heterozygous truncating variants in *NALCN* (MIM*611549), resulting in a loss-of- function (LoF) effect. *NALCN*-related disorders encompass a growing group of allelic conditions, including the autosomal dominant (AD) congenital contractures of the limbs and face, hypotonia, and developmental delay (CLIFAHDD, OMIM#616266), and the congenital ataxia with progressive cerebellar atrophy, camptodactyly, and hypertrichosis (CAPCACH) syndrome, delineating a phenotypic *continuum* of *NALCN* channelopathies.

**Methods**: We enrolled a new cohort of IHPRF1 patients within an international multicentric collaboration. Using dedicated *in silico* pathogenicity predictors and *ad hoc* structural analyses, we assessed the mechanistic consequences of the deleterious variants identified on NALCN structure and function.

**Results**: To date, 38 different *NALCN* variants have been retrieved from 33 different families (26 unrelated and 22 related patients). We report five new IHPRF1 patients from four unrelated families, harboring four newly identified and one previously reported variant that showed a markedly deleterious effect on channel stability and function, thereby compromising the functionality of the NALCN protein complex.

**Discussion**: By broadening the functional and molecular *spectrum* of biallelic *NALCN* variants, this study refines the IHPRF1 genotype–phenotype correlation and provides novel insight into the disorder's pathogenic mechanisms, strengthening its distinction within the *NALCN* channelopathy *spectrum* and supporting improved diagnostic and clinical management strategies.

**Key words:** NALCN, IHPRF1, CLIFAHDD, CAPCACH, channelosome complex, genotype-phenotype correlation, rhythmic behaviors, structural biology

## ID 29 POSTER PRESENTATION

### New Pathogenic RAI1 Variant in a Patient Presenting with Severe Behavioral Dysregulation in a Multidimensional Neurodevelopmental Profile: A Case Report

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**Background:** Smith–Magenis syndrome (SMS) is a rare neurodevelopmental disorder caused by 17p11.2 deletions or *RAI1* pathogenic variants. The availability of whole-genome sequencing makes it possible to gain a better appreciation for the phenotypic variability of the syndrome. We present a case illustrating that when intellectual disability is absent and behavioral problems are severe, diagnosis may be delayed, limiting timely access to tailored intervention.

**Case Presentation:** We report a 12-year-old boy with a multidimensional neurodevelopmental impairment ("Multidys" profile), including ADHD, autism spectrum disorder without intellectual disability, and developmental coordination disorder. Since age 3, he exhibited prolonged explosive outbursts, aggression, oppositionality, property destruction, hyperphagia with compulsive food seeking, and pica, leading to recurrent crises and extreme caregiver burden. During hospitalization, he was sexually assaulted by another patient, further increasing trauma vulnerability. Cognitive assessment showed preserved verbal abilities contrasting with profound adaptive and behavioral impairment. Whole-genome sequencing identified a new *de novo* heterozygous *RAI1* variant; chr17(hg38):g.17793789C>T c.841C>T (NM_030665.4) p.(Gln281*)). Multimodal intervention combining psychotropic medication and a highly structured therapeutic environment enabled partial stabilization and a safe discharge.

**Discussion/Conclusion:** RAI1-related SMS can manifest as severe, multidomain behavioral dysregulation despite preserved cognition. This case illustrates that *RAI1* variants may present primarily with extreme behavioral severity while intellectual functioning remains in the normal range. Early recognition of atypical SMS is crucial to avoid diagnostic delay, guide personalized intervention, and prevent family exhaustion. Genetic testing should be considered in complex, treatment-resistant behavioral disorders within the neurodevelopmental spectrum.

**Keywords:** Smith–Magenis syndrome; *RAI1*; behavioral dysregulation; multidimensional neurodevelopmental impairment

## ID 33 POSTER PRESENTATION

### Neuropsychological insights: Executive and social functioning in children and adults with Noonan syndrome

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**Introduction:** Noonan Syndrome (NS) is a rare genetic condition linked to various cognitive and behavioral vulnerabilities, particularly in executive functioning (EF) and social cognition (SC). These impairments can significantly affect daily functioning, learning, and social interactions. First, we present a study aimed at examining executive functioning (EF) and social cognition (SC) in children with NS, with the goal of deepening our understanding of their cognitive and behavioral profiles and informing potential treatment strategies. Additionally, we present two studies exploring the feasibility and preliminary effectiveness of eHealth interventions: one targeting EF in children, and the other focusing on SC in adults with NS.

**Methods:** In the first study, 26 children with NS (ages 7-17) were compared to 25 typically developing peers using cognitive and behavioral assessments. Multivariate analyses of variance were conducted, controlling for crystallized intelligence, to examine group differences. The second and the third study evaluated the feasibility and preliminary effectiveness of two eHealth interventions: (1) Braingame Brian (BGB), a computerized EF training, consisting of eight children in the treatment group and four children in the waitlist control group, and (2) eSENS, an online Social-Emotional training for adults with NS, involving 18 adults in the treatment group. Pre- and post-treatment assessments included neuropsychological tests and/or questionnaires on among others EF, SC, alexithymia, emotional self-efficacy, and emotion regulation.

**Results:** In the first study, children with NS showed significantly lower performance in working memory and attention compared to typically developing peers, along with more experienced EF problems, behavioural traits of ADHD and autism spectrum disorders. In the BGB pilot study, children demonstrated significant improvements in cognitive flexibility and inhibitory control within the trained tasks. However, no significant group-level differences were found between the treatment and waitlist control group on broader EF and SC measures. In the eSENS study, adults reported significant improvements in alexithymia, social-emotional self-efficacy, emotion regulation (more reappraisal, less suppression), and anxiety. Weekly assessments confirmed increased use of adaptive emotion regulation strategies. Proxies also reported reductions in alexithymia.

**Discussion/conclusion:** These studies collectively highlight the cognitive and social-emotional challenges faced by individuals with NS. Difficulties in working memory and attention are prominent in children with NS, often accompanied by behavioral traits linked to ADHD and autism spectrum disorders, and EF problems experienced in daily life. While the Braingame Brian pilot study showed task-specific improvements in cognitive flexibility and inhibition, these improvements did not generalize to broader executive or social functioning. In contrast, the eSENS intervention for adults demonstrated promising effects with respect to alexithymia, emotion regulation, social-emotional self-efficacy, and anxiety. Building on these outcomes, an interactive social-emotional training program for children and adolescents with NS is currently being developed. This initiative represents a valuable step toward improving emotion regulation and social skills in everyday life for young individuals with Noonan Syndrome.
Since EF and social cognition are vulnerable domains in various genetic syndromes—often linked to ADHD- and ASD-like behaviors—it is worth exploring whether elements of this training could benefit other genetic conditions as well.

**Key words**: Noonan syndromes, RASopathies, cognition, behaviour, social cognitive training



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## ID 34 POSTER PRESENTATION

### Neuropsychological insights: Koolen-de Vries syndrome and CAMK2-related syndromes

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**Introduction:** We present two studies investigating neuropsychological functioning in individuals with Koolen-de Vries Syndrome (KdVS) and CAMK2-related syndromes (CAMK2A and CAMK2B syndrome). Both conditions are associated with intellectual disability, developmental delays, and behavioral challenges, including anxiety, impulsivity, and autistic traits. Formal test-based studies in larger cohorts are currently lacking. To gain deeper insight into the relationship between cognitive impairments and psychopathological features, we hope to contribute to syndrome-transcending insights, ultimately enhancing care for individuals with rare neurodevelopmental disorders from a neuropsychological perspective.

**Methods:** In the ongoing KdVS study, adults (≥16 years) with a confirmed diagnosis complete an extensive neuropsychological assessment, including standardized cognitive tasks measuring intelligence, visuomotor skills, language, attention, executive functioning, memory, and social cognition. Caregivers complete questionnaires on adaptive functioning, emotional and behavioral regulation, sensory processing and caregivers' quality of life. In the ongoing CAMK2 study, caregivers of individuals of all ages with CAMK2A or CAMK2B variations complete questionnaires focusing on behavioral, emotional, sensory, and adaptive functioning. Emotional and behavioral functioning is further examined through semi-structured interviews, employing the K-SADS and DSM-5-derived items. Intellectual functioning is assessed using age-appropriate tasks or, when available, based on prior clinical evaluations. Results will be analyzed using age- and IQ-adjusted normative references, combining quantitative and qualitative approaches.

**Results:** Data are currently being analyzed and results will be presented during the EuroNDD-meeting. We will present cognitive and behavioral profiles, highlighting syndrome-specific trends as well as potential commonalities across the genetic syndromes

**Discussion/conclusion:** Through detailed cognitive and behavioral profiling, these studies aim to enhance understanding of daily functioning in individuals with KdVS and CAMK2-related syndromes, contributing to the development of diagnostic strategies, tailored care and treatment. Findings may also enhance a broader understanding of shared neuropsychological mechanisms across rare genetic conditions, supporting cross-syndrome approaches in both clinical practice and research.

**Key words:** cognitive phenotyping, Koolen-de-Vries syndrome, CAMK2-related syndromes, clinical neuropsychology

## ID 36 POSTER PRESENTATION

### A Novel TTI2 Variant: Expanding the Clinical Spectrum of Triple T Complex Disorder

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**Objective: TELO2 Interacting Protein 2 (*TTI2*)** is an essential component of the **Triple T (TTT) complex**, together with ***TELO2*** and ***TTI1***. The TTT complex plays a pivotal role in the folding, stabilization, and activation of the phosphatidylinositol 3-kinase–related kinase (PIKK) family, which regulates DNA damage response, telomere maintenance, and cellular growth. Disruption of this complex adversely affects neurodevelopment, resulting in a broad phenotypic spectrum that includes intellectual disability, developmental delay, and neurological abnormalities. We describe two male siblings from a consanguineous family harboring a novel biallelic TTI2 variant, further delineating the phenotypic spectrum of TTT-complex–related neurodevelopmental disorders (NDDs).

**Methods**

**Case Presentation:** Case 1: An 8-year-old male (birth weight: 3100 g) required neonatal intensive care for respiratory distress. Developmental milestones were markedly delayed (head control 12 mo, independent sitting 24 mo, walking and first meaningful word at 4 yr). Epileptic seizures began at 1 yr. Physical findings included trigonocephaly, high nasal bridge, small low-set ears, bilateral cryptorchidism, pes planus, and overriding toes. Anthropometric parameters were within normal range (weight SDS 0.67, height SDS 1.03, head circumference SDS 1.04). Brain MRI showed a thin corpus callosum.
Case 2: His 29-month-old brother (birth weight: 3200 g) presented with neonatal convulsions and respiratory distress. He exhibited global developmental delay, strabismus, and pectus carinatum, in addition to the features shared with his sibling. Growth parameters were reduced (weight SDS –4.7, height SDS –3.97, head circumference SDS –2.74). Brain MRI demonstrated a thin corpus callosum and hydrocephalus.

**Results:** Whole-exome sequencing identified a novel homozygous splice variant in TTI2 (c.1259+2dup), classified as likely pathogenic and associated with Intellectual Developmental Disorder, Autosomal Recessive 39 (MIM #615541).

**Conclusion:** The clinical findings in these siblings broaden both the phenotypic and molecular spectrum of TTI2-related neurodevelopmental disorders, underscoring the overlapping features observed among TTT-complex subunit defects (TTI1, TTI2, TELO2). The intrafamilial variability observed suggests differential tissue vulnerability to bioenergetic stress, potentially implicating mitochondrial or metabolic pathways downstream of TTT dysfunction.
To advance understanding of this rare disease group, systematic multicenter aggregation of TTT-complex–related cases is crucial for detailed genotype–phenotype correlation and pathway-level analyses. Further functional investigations focusing on mTOR–ATM signaling, mitochondrial stress response, and energy metabolism may provide valuable insights into the molecular mechanisms linking TTT complex dysfunction to neurodevelopmental pathology.

**Keywords:** TTI2, Triple T complex, neurodevelopmental disorder, genotype–phenotype correlation, mitochondrial stress

## ID 37 POSTER PRESENTATION

### Long-Term Follow-Up in Two Siblings with CODAS Syndrome

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**Objectives:** Cerebral–Ocular–Dental–Auricular–Skeletal (CODAS) syndrome is a rare autosomal recessive multisystem disorder caused by biallelic pathogenic variants in *LONP1*, which encodes a mitochondrial AAA$^+$ protease essential for maintaining mitochondrial proteostasis and respiratory chain integrity. Dysfunction of this enzyme primarily affects tissues with high energy demand—such as the cerebellum, ocular lens, and growth cartilage—leading to developmental delay and ataxia. Longitudinal clinical and radiologic data remain limited. Here, we report two siblings homozygous for a novel *LONP1* variant (c.1174C>T), emphasizing their extended clinical and neuroimaging follow-up over a three-year period.

**Methods:** Both siblings were born to healthy consanguineous parents. Comprehensive multidisciplinary evaluations were performed from 2022 to 2025, including serial neurological, endocrinologic, ophthalmologic, audiologic, and developmental assessments. Growth parameters were expressed as standard deviation scores (SDS). Serial brain MRI studies were analyzed for cerebellar volume loss, cortical signal abnormalities, and progression of structural changes.

**Results:** Case 1: A 6-year-old female, born at term (birth weight 3000 g), had normal early development (head control at 2 mo, sitting at 7 mo, walking at 12 mo, first words at 1 yr). At 2.5 yr, she developed gait instability and right-sided tremor, progressing to ataxia that later stabilized. At her most recent evaluation (6 yr 1 mo), weight was 15 kg (SDS –2.31), height 103.5 cm (SDS –2.57), and head circumference 47.2 cm (SDS –2.75). She exhibited truncal and limb ataxia, dysmetria, intention tremor, and mild dysarthria, but tone and reflexes were preserved. Speech, cognition, and social interaction were appropriate. Ophthalmologic evaluation revealed postoperative bilateral cataracts with residual visual impairment; hearing was normal. MRI (2022–2025) showed cerebellar atrophy and cortical T2/FLAIR hyperintensities without progression. Echocardiography revealed a small patent ductus arteriosus and secundum atrial septal defect. Growth and systemic findings remained stable throughout follow-up.

Case 2: A 9-year-old female, born at term (birth weight 2500 g), had delayed milestones (head control 2 mo, sitting 7 mo, walking with support 24 mo, first words 2 yr). Epileptic seizures began at 5.5 yr and were well controlled with valproate. At her latest evaluation (9 yr 5 mo), weight was 18 kg (SDS –3.08), height 117.5 cm (SDS –2.85), and head circumference 48 cm (SDS –3.07). She showed independent walking, truncal and limb ataxia, dysmetria, and fine motor discoordination, with preserved tone and social engagement. Speech was dysarthric but communicative. MRI (2021–2025) revealed diffuse cerebellar atrophy and cortical T2/FLAIR hyperintensities, stable over time. Ophthalmologic and audiologic evaluations were normal, and endocrine testing for short stature was unremarkable. Aside from one episode of dental osteomyelitis, no systemic involvement was detected.

**Conclusion:** These two siblings illustrate that CODAS syndrome may follow a slowly progressive but functionally stable neurological course, with radiologically stable cerebellar atrophy and cortical signal changes over several years. Despite early neurodevelopmental involvement, growth and systemic homeostasis remained stable, suggesting possible postnatal compensatory mitochondrial adaptation. This longitudinal follow-up provides one of the most detailed characterizations of clinical–radiologic stability in CODAS syndrome and contributes valuable insight into its natural history and phenotypic evolution. Larger, long-term multicenter studies are needed to better define the progression and variability of LONP1-related disorders.

**Keywords:** CODAS syndrome, LONP1, mitochondrial disorder, cerebellar atrophy, longitudinal follow-up

## ID 38 POSTER PRESENTATION

### Beyond The Classical Triad: Rare Features And Multidisciplinary Insights From Five Sotos Syndrome Patients

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**Introduction:** Sotos syndrome (OMIM #117550, ORPHA:821) is a rare genetic overgrowth disorder caused by heterozygous *NSD1* likely pathogenic or pathogenic variants. It is characterized by a distinctive facial gestalt (broad prominent forehead, dolichocephalic head shape, sparse frontotemporal hair, down-slanting palpebral fissures, malar flushing, long and narrow face, pointed chin), overgrowth (height and/or head circumference ≥2 SD above the mean), and neurodevelopmental delay of variable degree. We present a clinical and molecular overview of five unrelated Lithuanian patients diagnosed at LUHS Kaunas Clinics, emphasizing both classical and atypical findings and exploring possible genotype–phenotype correlations.

**Methods:** Comprehensive multidisciplinary evaluations were performed in all patients. Whole-exome sequencing (WES) confirmed heterozygous *NSD1* likely pathogenic variants. Parental segregation analysis was carried out when possible.

**Results:** The cohort comprised five unrelated patients (three males and two females) with molecularly confirmed Sotos syndrome. The mean age at the last evaluation was 4.8 (SD 3.0 years). All cases were sporadic (parental testing confirmed in 3/5 cases). Three frameshift variants in the *NSD1* gene (NM_022455.5): c.4670dup (p.Leu1557Phefs*3), c.3931del (p.Arg1311Alafs*8), c.8058del (p.Ser2687Valfs*74) and two missense variants: c.6128T>C (p.Phe2034Ser), c.6107G>A (p.Gly2036Glu) were identified. All patients exhibited the classical triad of Sotos syndrome — overgrowth, distinctive facial gestalt, and developmental delay. The mean height was +3.1 (SD 0.6) and the mean head circumference +2.7 (SD 0.5), confirming consistent overgrowth. Hypotonia and neonatal feeding difficulties were observed in 4/5 (80%) patients, ventriculomegaly in 4/5 (80%), cardiac anomalies in 2/5 (40%), and behavioral or cognitive issues in 2/5 (40%). Macrocephaly was present in 2/5 (40%) patients. One patient presented with craniosynostosis, a rare finding in Sotos syndrome. Seizure activity or epilepsy was documented in 2/5 (40%) patients: one had transient seizures without a confirmed epilepsy diagnosis, while another had confirmed epilepsy. No distinct clinical differences were observed between patients with frameshift and missense variants.

**Discussion:** Our findings confirm the classical phenotype of Sotos syndrome while also highlighting less common manifestations, such as seizures/epilepsy (in literature up to 50%) and craniosynostosis (10%). Neurodevelopmental outcomes in our cohort ranged from mild psychomotor delay to moderate, progressive intellectual impairment, emphasizing the importance of early neurocognitive assessment and individualized educational and rehabilitative support. No correlation was observed between variant type (frameshift vs. missense) and clinical severity, consistent with prior literature. Given the wide range of comorbidities, multidisciplinary and follow-up is essential, with special attention to late-emerging seizures and behavioral challenges.

**Conclusion:** This series indicates the broad clinical spectrum of Sotos syndrome. Despite differing variant types, phenotypic severity was comparable. Variable neurodevelopmental outcomes highlight the importance of early, individualized neuropsychological and educational support. Multidisciplinary follow-up remains crucial to ensure optimal long-term outcomes.

**Keywords:** Sotos syndrome, *NSD1*, overgrowth, neurodevelopmental disorder, WES.

## ID 83 POSTER PRESENTATION

### A Genetically Unresolved Neurodevelopmental Disorder with Unusual Cutaneous Manifestations in a Consanguineous Palestinian Family

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Neurodevelopmental disorders (NDDs) constitute a clinically and genetically heterogeneous group of conditions often presenting with developmental delay, epilepsy, and variable systemic features.

**Case Presentation:** We describe a 9-year-old girl, the 5th child of healthy first-cousin parents, presenting with a complex neurodevelopmental disorder and unique dermatological manifestations. The patient was born at full term via cesarean section (birth weight 3000 g) following an uncomplicated pregnancy with normal fetal development and no teratogenic exposures. The neonatal period was notable only for temporary jaundice. The mother, 43 years old (G6P5A1), had no chronic medical conditions. The patient was the fifth sibling of healthy consanguineous parents (first cousins). Her three brothers and one sister are clinically unaffected, and the family history is otherwise unremarkable. Developmentally, she exhibited global developmental delay, was unable to walk independently (HP:0002540), could stand only with support, and had absent speech (HP:0001344), producing limited vocalizations. Fine motor skills were markedly impaired, with inability to hold objects. Neurological examination revealed axial hypotonia (HP:0008936) with peripheral spasticity, and failure to thrive (HP:0001508). Additional clinical features included congenital microcephaly (HP:0000252), poor visual tracking, intractable seizures, and periventricular calcifications confirmed on brain CT. Of particular note, her skin showed progressive involvement from 8 months of age, with multiple small hyperpigmented nodules and generalized hyperpigmentation, predominantly affecting the hands, feet, and axillary regions, a feature not typically described in common NDD phenotypes. Facial examination revealed coarse features, synophrys, thick eyebrows and eyelashes, full lower lip, and a bulbous nasal tip. There were no cardiac, pulmonary, abdominal, or genitourinary abnormalities.
Whole-exome sequencing (WES) revealed no pathogenic or likely pathogenic variants in genes known to cause NDDs or neurocutaneous syndromes, and no plausible candidate variants of uncertain significance were identified after bioinformatic filtering.

**Conclusion:** This case illustrates the complexity of genetically unresolved neurodevelopmental disorders, even in consanguineous families where a recessive etiology is likely. The constellation of microcephaly, intractable epilepsy, periventricular calcifications, motor impairment, and progressive cutaneous hyperpigmentation may represent a novel or ultra-rare syndromic entity. Comprehensive genomic approaches such as whole-genome sequencing or transcriptome analysis may be required to uncover noncoding or structural variants responsible for this phenotype.



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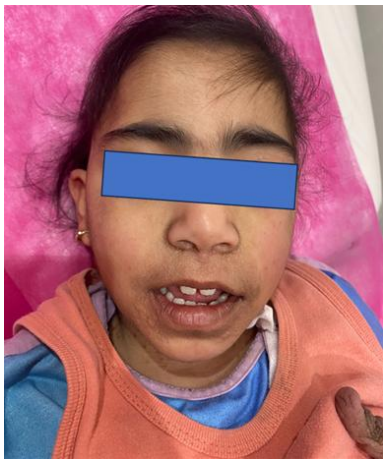

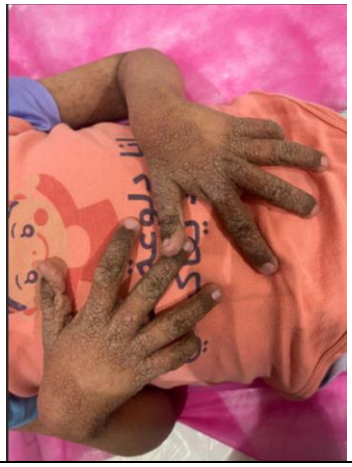

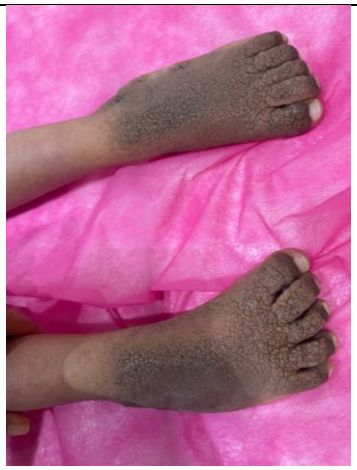

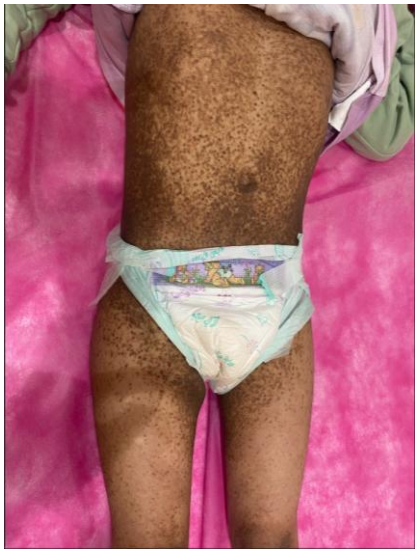

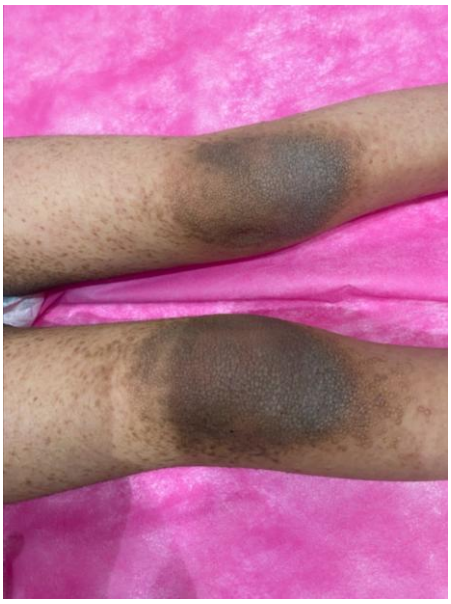

The Clinical images are published with parental consent. Identifiable features have been obscured to preserve patient anonymity.



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## ID 32 POSTER PRESENTATION

### A case of 17p13.3 microduplication with global developmental delay, dysgenesis of the corpus callosum, and multiple congenital anomalies: diagnostic challenges and genetic insights

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**Introduction:** We present a 1-year-old patient with global developmental delay, facial dysmorphisms and multiple congenital malformations. He is the third child of a gravida 3, para 3, was born preterm at 34 weeks of gestation with a birth weight of 1700 g and length of 47 cm. The neonatal period was complicated by congenital pneumonia. Throughout infancy, the patient experienced recurrent hospitalizations due to severe malnutrition and respiratory illnesses, including two episodes of pneumonia and two episodes of acute obstructive bronchitis. On endocrine evaluation, the patient was diagnosed with secondary hypothyroidism. Additional findings included left communicating hydrocele, exocrine pancreatic insufficiency and severe pediatric obstructive sleep apnea-hypopnea syndrome characterized by marked nocturnal hypoxemia. Ultrasound examination revealed left renal agenesis with absence of the left renal artery, cystic dysplasia of the right kidney and urolithiasis. Neurological assessment demonstrated significant motor developmental delay. MRI of the brain showed dysgenesis of the corpus callosum and retrocerebellar cyst.
At the time of the latest consultation, the following features were observed: weight – 3190 g (< 1 percentile, -7.2 SD), height – 62 cm (< 1 percentile, -5.48 SD), head circumference (< 1 percentile, -4.64 SD), dolichocephaly, prominent forehead, downslanted palpebral fissures, von Graefe sign, upturned nasal tip, wide nasal ridge, low-set ears, short neck, pectus carinatum, single transverse palmar crease.

**Methods:** The patient was referred to a geneticist for further confirmation of diagnosis. Conventional karyotyping, array comparative genomic hybridization (array CGH), and whole-exome sequencing (WES) were performed. Karyotyping was carried out using standard GTG-banding techniques at a 500-band resolution. Array CGH was performed using the Cytoscan 750K kit, GeneChip system 3000 7G Microarray. Whole-exome sequencing (WES) was performed using the Vazyme WES Library Prep Kit according to the manufacturer's protocol, and sequencing was conducted on an Genolab-M platform with a minimum average coverage of 100×. Data were analyzed using standard bioinformatics pipelines for variant calling and annotation.

**Results:** First, karyotyping was performed, which revealed a normal 46,XY karyotype.
Subsequently, the patient underwent array CGH and whole-exome sequencing (WES). The results of aCGH were arr[GRCh38] 17p13.3(2365018_3347100)x3, spanning 982082 bp and encompassing 8 genes: *PAFAH1B1* (607432), *SGSM2* (611418), *MNT* (603039), *CLUH* (616184), *RAP1GAP2* (618714), *OR1D2* (164342), *OR1A2* (618047), *OR1A1* (618046). Among these, *PAFAH1B1* is the most well-characterized gene, which is associated with lissencephaly 1 and subcortical laminar heterotopia, an autosomal dominant brain malformation disorder caused by defective neuronal migration during fetal development, leading to agyria or pachygyria. The remaining genes in the duplicated region have not been definitively linked to specific disease phenotypes.
WES results did not reveal pathogenic or likely pathogenic variants that could explain the patient's clinical phenotype, however, several variants of uncertain significance (VUS) were detected, including:

- ***BPTF*** gene missense SNV (c.8068C>T, p.P2690S). This variant has not yet been reported in the literature. However, pathogenic variants of BPTF are associated with a neurodevelopmental disorder with dysmorphic features and distal limb anomalies (NEDDFL) (OMIM #617755), an autosomal dominant disease characterized by developmental delay, facial dysmorphism, poor growth with small head size, and distal skeletal abnormalities.



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- ***FBN2*** gene missense SNV (c.2507C>T, p.T836M), the pathogenic variants of this gene are associated with Beals syndrome (OMIM #121050), an autosomal dominant connective tissue disorder.
- ***IGF1R*** gene splice region SNV (c.3722+4C>T), pathogenic variants are associated with Insulin-like growth factor I resistance (OMIM #270450). However, predictable tools suggest that this variant does not have significant deleterious effect.
- ***NOTCH1*** gene missense SNV (c.6383C>T, p.P2128L), pathogenic variants are associated with Adams-Oliver syndrome 5 (OMIM #616028), an autosomal dominant rare congenital disorder characterized by a combination of limb abnormalities and defects of the scalp. However, as with the previous gene, by predictable tools this varinat was suggested to not have significant deleterious effect.
- ***MAP2K1*** gene missense SNV (c.1008T>G, p.D336E), pathogenic variants are associated with Cardiofaciocutaneous syndrome (OMIM #615279), an autosomal dominant RASopathy characterized by global developmental delay, cardiac anomalies, hair and skin abnormalities, postnatal growth deficiency and hypotonia.
- ***NRXN3*** gene splice donor SNV (c.4014+2T>G) (600567)
- ***KMT2D*** gene missense SNV (c.13139C>T, p.P4380L), pathogenic variants are associated with Kabuki syndrome 1 (OMIM #147920), an autosomal dominant disorder characterized by developmental delay, distinctive facial dysmorphism postnatal growth deficiency and variable congenital malformation.

**Conclusion:** All identified genetic findings can partially explain the patient's phenotype, particularly the neurodevelopmental delay and brain structural abnormalities. Nevertheless, the underlying cause of the renal malformations remains unclear, as none of the detected variants have been previously reported in association with renal anomalies in the medical literature. To better define the genetic etiology of the unresolved congenital anomalies, additional investigations such as whole-genome sequencing (WGS) and DNA methylation profiling should be considered to detect potential epigenetic or regulatory abnormalities not captured by previous analyses.

**Keywords:** global developmental delay, congenital anomalies, 17p13.3 microduplication, renal malformations, neurodevelopmental delay, dysgenesis of the corpus callosum

## ID 35 POSTER PRESENTATION

### Allelic Missense Variants in FGF13A: Same Site, Different Syndrome, and a Caffeine Fix

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**Introduction:** Hemi- or heterozygous missense variants in FGF13 isoform A (FGF13A) are associated with X-linked dominant epileptic encephalopathy (DEE). Affected individuals present with severe developmental delay and therapy-resistant epilepsy. FGF13A is one of five FGF13 isoforms and is highly expressed in both inhibitory and excitatory neurons. Its unique N-terminus contains a 21 amino acid inactivation particle that mediates blockage of voltage-gated sodium channels ($Na_V$). All DEE variants lie within this domain and impair $Na_V$ inactivation, leading to increased neuronal excitability and epilepsy.

**Methods:** We performed exome/genome sequencing in a cohort of movement disorder patients.

**Results:** We identified three novel hemizygous, pathogenic missense variants in FGF13A in four unrelated males with a distinct clinical phenotype: severe paroxysmal dyskinetic movement disorder (PxD) without epilepsy. All experienced paroxysmal events in infancy, initially misdiagnosed as epilepsy. However, repeated ictal EEGs were normal, leading to a diagnosis of kinesigenic and non-kinesigenic PxD. PxD consisted of both a hyperkinetic and hypotonic phase with a high attack frequency (60-100/day), lasting 3 to 5 min, thus significantly limiting daily activities.
Although PxD variants cluster in close proximity to the DEE variants within the inactivation particle domain, they display an X-linked recessive inheritance pattern, as carrier mothers are unaffected. Skewed X-inactivation was not observed. Electrophysiological investigation of one PxD variant revealed a pronounced alteration in the known inactivation and recovery kinetics of sodium channels. We could show that FGF13-mediated inactivation of ion channels was slower compared to the wild type, likely mediated by altered stability of the FGF-ion channel complex.



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PxD was unresponsive to conventional treatments including multiple antiepileptic drugs, ketogenic diet and a deep brain stimulation. Remarkably, caffeine showed partial efficacy in two patients, shortening the intensity and frequency of the hyperkinetic phase in one and the duration of the hypotonic phase in the other. In the latter, combination therapy with methylphenidate enhanced the caffeine effect and abolished the hypokinetic phase of some attacks.

**Conclusion:** Here, we report a novel genetic entity, the FGF13A-associated paroxysmal dyskinesia, which exemplifies the broad clinical and genetic heterogeneity of hereditary diseases. We highlight how a simple pharmacologic intervention can significantly improve quality of life, underscoring the importance of genetic diagnosis in personalised medicine.

**Key words:** FGF13, FGF13A, paroxysmal dyskinesia, PxD, caffeine, sodium channels

## ID 40 POSTER PRESENTATION

### DNA methylation episignatures in NDDs: expanding diagnostics, validating with nanopore, and future functional applications

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**Introduction:** DNA methylation episignatures have emerged as powerful tools for the molecular diagnosis of neurodevelopmental disorders (NDDs). They provide functional insight into the pathogenic mechanisms underlying both genetic and environmental etiologies. We aimed to explore episignatures across diverse NDDs, including those caused by sequence variants, copy number variants (CNVs), and teratogenic exposures, and to validate these molecular findings using complementary functional approaches.

**Methods:** Genome-wide DNA methylation profiling was performed on patient cohorts with (i) ubiquitination-related genes *TRIP12* and *USP7*, (ii) CNV-associated syndromes including *JARID2*, Smith-Magenis, and Potocki-Lupski syndromes, and (iii) fetal alcohol spectrum disorder (FASD). Long-read nanopore sequencing was applied to *USP7* cases to confirm pathogenic variants and to assess methylation concordance with array-based episignature data. Expression quantitative trait methylation (eQTM) analyses were conducted on fibroblast and whole blood samples to identify functionally relevant methylation–expression relationships. Additionally, patient-derived induced pluripotent stem cell (iPSC) lines were established from individuals with pathogenic *USP7* and *TRIP12* variants for future mechanistic studies.

**Results:** Distinct and reproducible DNA methylation episignatures were identified for each investigated condition, expanding the current catalogue of molecularly diagnosable NDDs. Nanopore sequencing confirmed accurate variant detection and produced methylation profiles concordant with array-based data. eQTM analyses revealed gene-specific methylation–expression associations supporting functional relevance of identified loci. The generation of iPSC models provides a foundation for downstream cellular and mechanistic investigations.

**Discussion/Conclusion:** Our integrated genomic and epigenomic approaches demonstrate the diagnostic and translational potential of episignatures in NDDs. These studies bridge genetic, CNV-related, and teratogenic mechanisms, facilitating precision molecular diagnostics and enabling functional exploration of disease biology. Together, these findings advance the implementation of episignature-based testing as part of state-of-the-art diagnostic pipelines for rare neurodevelopmental conditions.

**Key words:** DNA methylation, Episignatures, Neurodevelopmental disorders, Precision diagnostics, functional studies



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# Health Information System and Data Availability

*-abstracts-*

*In dept discussion of Abstracts ID 43 + 44 in the breakout session Building Patient Registries under the GDPR – The Good, the Bad and the Ugly (an educational session followed by a roundtable discussion on Thursday afternoon)*

## ID 43 POSTER PRESENTATION

### FindMe2care: a contact platform for patients with confirmed genetic diagnoses

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**Introduction:** Identifying suitable participants remains a major challenge for research projects on genetic disorders, particularly in the context of rare disorders. To address this, FindMe2care was launched in 2024 as a not-for-profit platform designed to facilitate the contact and potential recruitment of patients with genetically confirmed diagnoses.

**Methods:** Patients diagnosed with a monogenic disorder receive a personalized QR code from their genetic laboratory, which securely encodes the details of their genetic report in a machine-readable format. Using this QR code, individuals can easily and accurately self-register on the platform, minimizing the risk of data transmission errors. Once registered, patients may be contacted by external parties seeking specific cohorts. All such inquiries - whether from researchers, specialized disease registries or patient organizations - are first reviewed by an independent scientific advisory board before being forwarded to eligible patients.

**Results:** Since the platform's inception >600 patients with 349 unique OMIM diagnoses registered themselves using QR-codes provided by 5 participating laboratories. Additional laboratories from Germany have committed to incorporating FindMe2care QR codes into their reports in the near future. Registration is entirely patient-driven and voluntary. FindMe2care still received phenotypic and genetic data in the standardized PhenoPacket format, meeting the requirements of international research networks. This enables precise searches for patients based on clinical diagnosis, affected gene(s), age range, or sex. Owing to the high quality of laboratory-provided data via QR codes, even more granular identification is possible, down to the level of specific causative variants or specific HPO terms. Currently invitations to 12 specific disease registries, 2 studies and 3 patient organizations were forwarded to eligible patients and will be extended to any newly registered patients matching inquiry criteria.

**Conclusion:** FindMe2care acts as a trusted data intermediary for patients wishing to participate in basic or clinical research and benefit from personalized treatments, ultimately aiming to improve care for genetic disorders. To broaden the platform's scope and impact, we welcome participation from genetic laboratories across other European countries to provide FindMe2care QR codes to their patients.

**Key words:** Patient recruitment, PhenoPacket, patient empowerment



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*In dept discussion of Abstracts ID 43 + 44 in the breakout session Building Patient Registries under the GDPR – The Good, the Bad and the Ugly (an educational session followed by a roundtable discussion on Thursday afternoon)*

## ID 44 POSTER PRESENTATION

### Privacy and Data Protection Issues in Creating a Rare Disease Patient Registry : Experiences from RettX

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**Introduction:** People with rare diseases and their communities can benefit enormously from the collection of their personal data in a registry. Such registries can be of benefit for themselves, for researchers developing therapies, and for comparative work between rare diseases. By including life experiences of participants in the registries, and curating those stories over time, the registry itself can become a longitudinal study of the experience of the disease and social responses to it. The creation of the **RettX patient registry**, a family-led European initiative for Rett Syndrome, is used as a case study to examine the legal and ethical challenges surrounding privacy and data protection.

**Methods:** The work underpinning this project is two-fold : 1) legal doctrinal and ethics analysis ; and, 2) qualitative enquiry of people with Rett syndrome. [The fieldwork is undertaken under the scrutiny of the Ethics Committee of The City Law School, City St George's, University of London.]

**Results:** The work is ongoing. Rett X is a Europe-wide registry. The key law is the European Union General Data Protection Regulation (2016/679), and the national implementation of that Regulation in the EU Member States. The preliminary work of the project shows that there is a lack of clarity in key concepts and terms in the GDPR. For example, there is a need for clarification in the definitions of, in the Data Protection Principles (Art. 5) « transparency », « compatible » processing, and « data minimisation » ; and, in the legal bases for processing (Art. 6) « informed consent » and « public interest ». Particular work is needed in clarifying the operation of the law in relation to secondary processing across the EU. It is unclear, when creating a registry, whether informed consent for compliance with the Data Protection Regulation is required to satisfy the individual Supervisory Authorities and relevant Research Ethics Committees.

Further, the underpinning concepts of Privacy and Property also lack clarity. There are differences in the Privacy sensitivities of different stakeholders engaged by the creation of registries. There is confusion about the ownership of personal data held in the registry.

**Discussion:** Whereas there is a lack of clarity in the concepts and key elements of the law in this area, it is possible to create sector-specific codes under the GDPR (Art. 40). There are routes that can be taken through the GDPR that optimise the functionality of registries for those with rare diseases whilst at the same time providing robust safeguards to the participants in the registry. Further, these routes better resonate with the expressed sensitivities of those wishing to participate in the registries (or of their guardians). By refocusing our understanding of both the underpinning concepts of the law and ethics, and the interpretation of the existing detail of the GDPR, it is possible to create and operate effective and useful registries in rare disease communities and between such communities.

**Key words:** Data Protection – Privacy – Patient Registries – Rett Syndrome – Property – Law and Ethics.



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## ID 45 ABSTRACT

No poster presentation, but integrated in the breakout session "**Measuring what matters in genetic neurodevelopmental disorders: trials and care" (Friday afternoon)**

### Toward better measurement in genetic developmental disorders: a systematic review of measurement properties

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**Introduction:** Many different outcome measurement instruments (OMIs) are used in clinical trials involving individuals with genetic neurodevelopmental disorders and intellectual disability (GND/ID). A recent scoping review identified 91 different outcomes measured with 457 different OMIs, highlighting substantial heterogeneity. This study aimed to systematically evaluate the measurement properties of the most commonly used OMIs in individuals with GND/ID, with a focus on patient-reported outcome measures (PROMs).

**Methods:** Measurement properties of OMIs used in ≥5 clinical trials were evaluated. MEDLINE and PsycINFO were searched to identify studies reporting on OMI development or evaluating at least one measurement property. We used the COSMIN (COnsensus-based Standards for the selection of health Measurement INstruments) guideline for systematic reviews of PROMs to appraise eligible studies. This included a risk of bias assessment of studies, an evaluation of measurement properties' results, and grading the quality of the evidence. When multiple studies addressed the same measurement property for the same PROM, results were synthesized descriptively. For non-PROM instruments, we summarized the evidence on measurement properties without a systematic evaluation.

**Results:** In total, 42 OMIs were used in at least 5 clinical trials. Of these, 12 were non-PROMs and their measurement properties will only be summarized, whereas for PROMs, the measurement properties will be systematically evaluated. Data extraction and synthesis are ongoing; results will be presented at the conference.

**Discussion/conclusion:** This systematic review will identify which OMIs demonstrate sufficient measurement properties and can be recommended for use in individuals with GND/ID, and which OMIs require further evaluation or should not be used at all. These results will inform consensus on a standard set of OMIs that are valid, reliable and responsive to change. This will facilitate more standardized outcome measurement in individuals with GND/ID.

**Key words:** Systematic review; genetic neurodevelopmental disorders and intellectual disability; measurement properties; COSMIN; outcome measurement instruments; patient-reported outcome measures (PROMs)



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## ID 47 POSTER PRESENTATION

### Diagnostic of FMR1 premutation in a cohort of children with neurodevelopmental disorders: definition of a clinical phenotype for pediatric population

Carme Torrents[1], Neus Baena[2], Violeta Fariña[1], Carmen Manso[2], Ariadna Ramírez[1], Lorena Joga[1], Ana Roche[1]

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**Introduction:** The clinical and neuropsychiatric profile associated with the premutation (PM; 55-200 CGG) of *FMR1* gene is poorly known in pediatric population, despite the estimated prevalence of this condition is 1/180 women and 1/400 men. The purpose of this project is to evaluate the prevalence of FMR1 PM in a cohort of children with different neurodevelopmental disorders (NDD) and to characterize the clinical phenotype of this condition.

**Methods:** Descriptive, observational, retrospective study of a cohort of children with NDD, with genetically confirmed PM condition, from the outpatient Pediatric Neurology Clinic

**Results:** A sample of 12 children was collected: 57% were male, 50% presented less than 70 CGG repeats, (55-147). Age of detection of PM was 5.18 ± 2.6 years. Regarding clinical phenotype, 70% presented autism spectrum disorder (ASD), 46% language impairment, 38% attention deficit hyperactivity disorder (ADHD), 15% intellectual disability (ID), and 15% borderline intellectual functioning. One patient had epilepsy. Anxiety signs were present in 57%

**Conclusions:** Premutation is a condition that, although more prevalent than FXS, is probably underdiagnosed and poorly understood. *FMR1* gene testing should be requested in every patient diagnosed with ASD or ID, especially if associated with anxiety or if family history is suggestive of genetic alteration of *FMR1*. Establishing a registry of children with premutation is necessary for a more comprehensive categorization of the clinical and neuropsychiatric phenotype associated.

**Key words:** autism spectrum disorder (ASD), neurodevelopmental disorder (NDD), Attention Deficit with /without Hyperactivity (ADHD), *FMR1*, premutation



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## ID 48 POSTER PRESENTATION

### Natural History Study of a cohort of Spanish patients: interim analysis focused on epilepsy and sleep

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**Introduction**: Angelman syndrome (AS) is a rare neurodevelopmental disorder cause by the absence of ub3a protein or loss of expression of maternal *UBE3A*, leading to intellectual disability, absence of verbal language, motor disturbances, epilepsy and sleep disorders, among others. Sleep and epilepsy are interrelated, and strongly influence the quality of life of children with AS. Moreover, knowing the natural history of epilepsy and sleep disorders in AS is crucial to evaluate the benefits of recent potential disease-modifying treatments.

**Methods:** Descriptive, observational, prospective study of a cohort of 40 children and adults with AS, with different genotypes, from the AS Clinics of Puerta del Hierro Hospital in Madrid and Parc Taulí Hospital in Sabadell, Spain. Data are collected during 2 years with the support of FAST-Spain.

**Results**: This interim analysis focuses on epilepsy and sleep profile of 40 patients with AS, describing age at epilepsy onset, types of seizures, response to different antiseizure medication (ASM), EEG patterns, including some especial conditions as Continuous spike-wave during sleep (CSWS), correlation with sleep (through actigraphy and questionnaires), and with quality of life of patients and their families.

**Conclusions:** Epilepsy in AS is very frequent and heterogeneous. Unsuspected CSWS may be more frequent in AS population and interfere sleep and quality of life. EEG combined with actigraphy and sleep questionnaires is an important tool to rule out non-motor epileptic activity and avoid clinical deterioration.

**Key words**: Angelman syndrome (AS), epilepsy, sleep disorders, actigraphy, quality of life, natural history.

## ID 50 POSTER PRESENTATION

### Follow-up of a 16-months old baby assessed with ADNP syndrome: does a very early genetic assessment allow an effective preventive multidisciplinary work ?

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**Introduction**: Described in 2014, the activity-dependent-neuroprotective-protein (ADNP) syndrome, caused by a de novo mutation, combines a neurodevelopmental delay and/or autism spectrum disorder (ASD) with multiple body organ involvements. (of note, there is a hope of genetic therapy, which evaluation will begin with children more than 6 years old). We previously reported the case of a 16-months-old baby diagnosed through a genomic sequencing launched because of a strong axial hypotonia. Weekly psychomotricity began at 8 months and physical therapy from 12 months on to sustain her motricity. Speech therapist's assessment was made at 13 months for chewing difficulties. As the family worried about some relational withdrawal, and baby being absorbed in her hands, assessment revealed communication delay and a lack of initiation in interaction, leading to weekly speech therapy sessions. Finally, when the ADNP diagnosis was made, the family solicited our pedo-psychiatric team. As we met her, the child was already progressing in motor and interactive abilities, with good though too brief moments of pleasure in interaction. However, the parents complained they did not feel their child looked at them enough.
Knowing the importance of autistic risk in this genetic disease, we decided to be attentive to this parental feeling and while completing the developmental assessment, to simultaneously complete without waiting the multi-disciplinary care with a parent-child interactive work specifically designed for children at-risk of ASD.
We aim to discuss if a very early diagnosis of a genetic disorder associated with risk of ASD gives a chance to intervene in prevention of ASD trajectory.

**Methods** We proposed a preemptive clinical integrative work, taking into account specificities of sensori-motor difficulties. Initial assessment was made at 18 months with the Bayley-4 scale. Orthophonic assessment and a Dunn profile completed the evaluation. In addition with the CAMSP multidisciplinary work with psychomotricity and orthophonic rreducation, a specific work was proposed to prevent ASD. It comprised a medical parental guidance and PACT sessions. At 3 years, assessment was made through VABS-2, and will be completed at 3;5 years with Bailey-4, ADI-R and ADOS.

**Results**: We will present initial and outcome assesments, describing intellectual deficiency and ASD initial risk in this baby, trajectory and outcome at 3,5 years of our clinical case, to discuss the effects of our multidisciplinary preemptive work.

**Discussion/Conclusion:** We will discuss, beyond this clinical case, the efficacy of a very early and intensive intervention to counter the bad neurodevelopmental prognosis of this genetic anomaly, within sustaining the parent-child interaction, modifying the at-risk interactive trajectory of the child, and allowing the cerebral brain to develop for the best.

**Keywords:** Neurodevelopment; Case Report; ADNP syndrome; autistic risk; prevention; multidisciplinary care



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## ID 51 POSTER PRESENTATION

### The use of the Computer-Based instrument for Low motor Language Testing (C-BiLLT) in children with complex communication needs due to rare genetic disorders

Cindy Navis[1], Dr. D. Hagenaar[1], A. van Hattem[1], Dr. G.C.B. Bindels – de Heus[1], Dr. M.C.Y. de Wit[1]

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**Introduction:** Standardized assessments of language comprehension pose significant challenges for children diagnosed with Angelman Syndrome and Dup15Q syndrome, due to their complex communication needs and motor limitations. The Computer-Based instrument for Low motor Language Testing (C-BiLLT), originally developed for children with cerebral palsy, has since its release also been used for children and (young) adults with other diagnoses and complex communication needs (CCN).

**Method:** This study is part of a larger natural history cohort study, 27 children (2-18 years) with Dup15Q syndrome and 65 participants with Angelman Syndrome (2-19 years) were evaluated as part of their regular follow-up schedule and standard care at the ENCORE Expertise centers. Since 2017, the C-BiLLT has been implemented in the Sophia Children's Hospital ENCORE as the standard instrument for evaluating receptive language in children with complex communication needs resulting from rare genetic conditions. The C-BiLLT comprises 88 items designed to assess comprehension of spoken language. All assessments were conducted by C. Navis, a speech and language therapist trained in the administration of the C-BiLLT by its developer, Dr. J.J.M. Geytenbeek.

**Results:** The majority of participants were able to complete at least one item of the C-BiLLT, and the distribution of scores demonstrated substantial variability. This supports the instrument's sensitivity to individual differences and its potential utility in tracking developmental progress over time. Preliminary data from the Dup15Q cohort revealed marked heterogeneity in communicative abilities, underscoring the need for individualized assessment approaches.

**Conclusion**: The findings of this study indicate that the C-BiLLT is a feasible and informative tool for assessing language comprehension in children with Angelman Syndrome and Dup15Q syndrome. Given its accessibility and adaptability, we advocate for its use in both clinical practice and research settings. Translations of the C-BiLLT are currently available in several languages, including English and German, facilitating broader international implementation.

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## ID 52 POSTER PRESENTATION

### From Gene to Communication: Translating Neurogenetic Profiles into AAC-Based Communication Interventions in Rare Neurodevelopmental Syndromes

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Advances in molecular genetics have significantly improved the diagnostics of rare neurodevelopmental syndromes. However, **translational pathways** — from genetic mechanisms to measurable outcomes of communication interventions — remain poorly understood.

This paper presents an attempt to develop an **interdisciplinary analytical mode**l linking neurobiological mechanisms associated with specific genotypes to communication profiles and the practice of communication interventions based on Augmentative and Alternative Communication (AAC).
The analysis covers four syndromes with distinct genetic etiologies:

- Angelman syndrome (UBE3A),
- Rett syndrome (MECP2),
- Down syndrome (trisomy 21), and
- Fragile X syndrome (FMR1).

For each condition, genotype–phenotype relationships were mapped in relation to characteristic communication profiles and priority areas of intervention within speech-language pathology, pedagogy, and psychology.

The findings indicate that linear developmental models (e.g., Piagetian stages) fail to capture the dynamics of communication development in genetic syndromes. Instead, **interactional and relational models — supported by AAC and partner-assisted communication strategies** — prove to be more effective, enabling the development of communicative competence despite sensorimotor or cognitive limitations.

The proposed model is **translational** in nature: it supports early, genotype-informed planning of communication interventions and promotes interdisciplinary collaboration among geneticists, speech-language pathologists, educators, and psychologists. It emphasizes that understanding molecular and neural mechanisms should serve not only diagnosis but also the **direct design of communicative and educational actions**.

**Keywords**
genetic neurodevelopmental disorders, Augmentative and Alternative Communication (AAC), communication intervention, genotype–phenotype correlation, Down syndrome, Angelman syndrome, Rett syndrome, Fragile X syndrome



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## ID 53 POSTER PRESENTATION

### *Botulinum Toxin Treatments in Children and Adults with Profound Intellectual and Multiple Disabilities (PIMD) in the Netherlands: Sense or Nonsense?*

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**Introduction**: Children and adults with profound intellectual and multiple disabilities (PIMD) represent a highly vulnerable group within healthcare. Spasticity, dystonia, and other movement disorders are common and can lead to discomfort, pain, limitations in mobility, and reduced quality of life. Botulinum toxin (BoNT) is widely used in treating neurological movement disorders, yet its use in the PIMD population remains controversial due to challenges in evaluation and outcome assessment.

**Methods**: Case series are conducted. We also intend to do a narrative literature review, supplemented by clinical experience from rehabilitation physicians and interdisciplinary care teams in long-term care-settings. Semi-structured interviews with caregivers and healthcare professionals to capture practical and ethical perspectives on the use of BoNT in this population can also be very valuable.

**Results**: BoNT may reduce spasticity, discomfort and pain in carefully selected cases. However, evaluating treatment effectiveness is complicated by limited communication abilities and the complex clinical profiles of individuals with PIMD. Treatment goals vary significantly—ranging from improving comfort to enhancing function—resulting in diverse interpretations of what constitutes therapeutic success. There is a link to the functional context. The results are not always objective, but are also subjectively queried with parents/caregivers; for example, the burden of ADL care as an influence on the child. The involvement of caregivers and interdisciplinary discussion is essential for appropriate decision-making.

**Discussion/Conclusion**: BoNT treatment can be meaningful for individuals with PIMD when based on clear, individualized goals. However, the line between therapeutic benefit and overtreatment is thin. Ethical considerations and realistic expectations must guide clinical decisions. Ongoing research is necessary to identify individuals that benefit most from BoNT treatment.

**Keywords:** Botulinum toxin, severe multiple disabilities, PIMD, spasticity, neurodisability, ethics, quality of life

## ID 54 POSTER PRESENTATION

### *Autosomal Recessive Intellectual Developmental Disorder Type 67 (MRT67) Associated with EIF3F c.694T>G (p.Phe232Val): Case Series and Perspectives for Translational Research*

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**Introduction:** Autosomal recessive intellectual developmental disorder type 67 (MRT67; MIM #618295) is a recently described neurodevelopmental condition caused by biallelic variants in the *EIF3F* gene (*Eukaryotic Translation Initiation Factor 3 Subunit F*; OMIM *603914*). The EIF3 complex plays a key role in translation initiation and neuronal development. Fewer than 20 families have been reported worldwide. Here, we present six Polish patients from four unrelated families harboring a homozygous *EIF3F* c.694T>G (p.Phe232Val) variant, highlighting the phenotypic variability and ongoing translational research initiatives.

**Methods:** Patients underwent detailed clinical evaluation including neurological, metabolic, and neuropsychological assessment. Molecular testing comprised chromosomal microarray (aCGH), targeted NGS panels for intellectual disability and autism spectrum disorders, and/or whole-exome sequencing (WES). Variant classification followed ACMG guidelines, with cross-references to ClinVar, Franklin, and Varsome databases. Parental testing confirmed biallelic inheritance of the *EIF3F* variant.

**Results:** All six affected individuals were homozygous for *EIF3F* c.694T>G (p.Phe232Val).
Clinical features included intellectual disability (mild to moderate), speech delay, motor retardation, autistic features, oral and verbal apraxia, and feeding difficulties. Neurological findings encompassed abnormal muscle tone, impaired coordination, and praxis deficits. Behavioral features included emotional lability, echolalia, and limited autonomy in daily living skills.
Physical examination revealed mild but recurrent dysmorphic traits: round facial shape, long earlobes, short thumbs, and restricted hand supination. Additional findings included obesity with hepatic steatosis, scoliosis, and mild myopia. EEG and MRI findings, when available, were unremarkable.
Parents of all probands were heterozygous carriers, confirming autosomal recessive inheritance.

**Discussion/Conclusion:** These cases further confirm the pathogenicity of *EIF3F* c.694T>G (p.Phe232Val) and broaden the clinical spectrum of MRT67. Despite the shared genotype, phenotypic diversity across the four unrelated families suggests possible genetic or environmental modifiers influencing clinical outcomes.
In collaboration with the EIF3F Research Foundation (https://eif3fresearch.org), our group is launching cell-based functional studies utilizing patient-derived iPSC models to investigate EIF3 complex activity and screen for potential therapeutic compounds, including drug repurposing candidates.
We also aim to establish a patient-led registry and research network to strengthen international collaboration, facilitate data sharing, and accelerate translational research toward targeted therapies — both pharmacological and gene-based — for *EIF3F*-related neurodevelopmental disorders.

**Keywords:** *EIF3F*, MRT67, intellectual disability, autism spectrum disorder, iPSC, translational research, rare diseases, drug repurposing



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## ID 55 POSTER PRESENTATION

***Placing the person with a genetic neurodevelopmental disorder at the heart of the holistic care network: the experience of running focus groups with people with Rett syndrome in order to co-produce training and educational resources for multi-disciplinary teams.***

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**Introduction:** In Burden of Illness studies, communication difficulties are frequently reported to be one of the greatest challenges experienced by people with Rett syndrome and their caregivers. In recognition of this, the Rett Syndrome Communication Guidelines were published in 2020 with the aim of sharing information and establishing a baseline of good practice that can be expected by people with Rett syndrome and their families regardless of the country and situation in which they are living. Section Two of the guidelines stresses the importance of team working, with the recommendation that every individual with Rett syndrome be supported by a multidisciplinary team (MDT) whose members share a common vision and work collaboratively to define and agree on communication goals and support plans. Often, but not in all cases, a speech and language therapist (SLT) will be the key person who takes responsibility for monitoring those communication goals. In many instances, however, SLTs lack experience of, and expert knowledge about, Rett syndrome, and there are tensions between the views and opinions of the SLT and those of the person with Rett syndrome and their caregivers. One way of overcoming this is through the development of training and educational resources that supplement the communication guidelines; resources that can be used to enskill SLTs and other members of the team and that bring the views and opinions of all parties towards a closer understanding. Integral to the development of these resources is the idea of co-production: a process of working in partnership that rebalances the power between the professionals who provide services and those with lived experience who are in receipt of services.
This project aims to co-produce a comprehensive package of training and educational resources, using a collaborative process that includes people with Rett syndrome, their parents and other family members, and SLTs.

**Methods:** A series of three online focus groups/workshops will run in early 2026. The groups will comprise:

1. people with Rett syndrome supported by familiar communication partners;
2. parents/family members of people with Rett syndrome, who also work as part of the Rett UK Communication and Education Team (and who therefore have experience beyond the communication needs of their own family member);
3. SLTs who are members of a support group for SLTs working with people with Rett syndrome (the support group is run jointly by the University of Reading and Rett UK).

Each group will meet three times, with resource creation and testing between group meetings.
The project will be run with approval from the University Research Ethics Committee at the University of Reading.

**Results:** As the groups will be running in early 2026, the preliminary findings will be analysed and reported during the conference in April.

**Discussion/Conclusion:** Co-production with service users, their carers and families is one of the aspirations and main areas of focus written into the Royal College of Speech and Language Therapists' Strategic Vision 2022-2027 (RCSLT is the professional body for SLTs in the UK). To our knowledge this project will be the first of its kind that seeks to elicit the views and opinions of people with Rett syndrome and place them at the centre of development of training and educational resources for SLTs and other members of the MDT. The experience of utilising focus groups in this way can serve as a model for co-production of resources involving people with complex communication needs associated with other genetic neurodevelopmental disorders.

**Key words:** Rett syndrome, complex communication needs, speech and language therapy, teamwork, co-production, training and education, focus groups.



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## ID 56 POSTER PRESENTATION

### *Adult Emotional and Behavioural Patterns in Prader-Willis syndrome and Williams syndrome*

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**Introduction:** Prader-Willis (PWS) and Williams Syndrome (WS) are both multisystemic complex genetic disorders. PWS is caused by lack of expression of genes on the paternally inherited chromosome 15q11.2-q13 region. Short stature, developmental delay, cognitive disability and excessive weight gain is characteristic for the disorder. Behavioural problems are common, including food seeking behaviour, lack of flexibility, oppositional behaviours, interpersonal problems and abnormal emotional regulation.
WS is caused by deletion in the 7q11.23 region. The disorder is characterized by medical problems, including cardiovascular disease, developmental delays, and learning challenges.
While the elevated risk of mental and behavioural disorders in adulthood among individuals diagnosed with PWS and WS is recognized, the precise nature, scope, and variability of symptoms and functional impairments require further investigation
This study will assess adapted behaviour, challenging behaviour and psychiatric symptoms in adults (above 30 years old) in persons with either PWS or WS.

**Methods:** The study includes adults above 30 years old with either PWS or WS. We expect to include approximately 40 with PWS and approximately 40 with WS. We also have possibilities for approximately 40 controls matched for IQ from the BUPGEN registry.
Emotional and behavioural symptoms will be assessed using the Developmental Behaviour Checklist (DBC). The level of psychiatric symptoms will be assessed by using Psychopathology in Autism Checklist (PAC), a screening checklist designed to identify individuals with ID and autism spectrum disorder in need of psychiatric services. Adapted behaviour will be assessed by using Vineland Adapted Behaviour Scale.

**Results:** The data will be presented at the conference. We will present both Total and subscale scores on DBC, PAC and Vineland, and correlations between the different symptoms will be calculated.

**Key words**: Prader-Willis syndrome, Williams syndrome, aging, psychiatric symptoms, adaptive behaviour.



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## ID 58 POSTER PRESENTATION

### A rare variant of the ETF1 gene: Broadening the phenotypic spectrum and possible influence of early multidisciplinary management

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A rare variant of the ETF1 gene: Broadening the phenotypic spectrum and possible influence of early multidisciplinary management

**Background:** Pathogenic variants of the ETF1 (Eukaryotic Translation Termination Factor 1) gene have recently been associated with a rare neurodevelopmental disorder, generally characterized by global acquisition delay, intellectual disability, and growth retardation. This gene encodes a class-1 polypeptide chain release factor which plays an essential role in directing termination of mRNA translation from the termination codons UAA, UAG and UGA. Fewer than fifty cases are currently described in the international literature, and the phenotypic spectrum remains poorly defined.

**Case report:** We report the case of a 12-year-old female patient carrying a heterozygous variant of the ETF1 gene (chr5:g.138517583C>T c.380G>A (NM_004730.4) p.(Cys127Tyr) ), identified by exome sequencing, and followed by our department since early childhood. Unlike previously reported cases, she does not present with intellectual disability. However, she does present with several specific developmental disorders: developmental language disorder, developmental coordination disorder, and impaired executive functions. Growth retardation has also been noted since childhood with microcephaly and skeletal abnormalities. She received growth hormone last year. The current height is 132 cm (-2.3 SD), weight 25 kg (3rd percentile) and cranial perimeter 48.5 cm. Since age 1, she has had multidisciplinary care including speech therapy, occupational therapy, and neuropsychological monitoring.
She current attend a regular 6th grade class with several hours per week of a program for specific learning disabilities, with generally satisfactory performance.

**Discussion:** This observation expands the known phenotype of ETF1 gene abnormalities, suggesting that intellectual disability is not constant. The maintenance of preserved intellectual functioning raises questions about the potential role of early and coordinated intervention in the evolution of the phenotype. It is possible that multidimensional stimulation contributed to more favorable development and limited functional repercussions.

**Conclusion:** This case illustrates the clinical variability of ETF1-related disorders and highlights the importance of a detailed assessment and early multidisciplinary management, which can positively influence developmental outcomes.

**Key words:** ETF1 variant, phenotype, early multidimensional care and stimulation, developmental outcomes



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## ID 60 POSTER PRESENTATION

***"Mind the gap" –ERN ITACHA guidelines on transition from paediatric to adult healthcare system.***

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**Background:** For young people with rare conditions associated with intellectual disability, the transfer from paediatric to adult healthcare providers is often complicated. European Reference Network ERN-ITHACA (Intellectual disability, TeleHealth, Autism and Congenital Anomalies) on Rare Congenital Malformations and Rare Intellectual Disability aims to develop a clinical practice guideline to improve this transition. The aim of this study was to identify which aspects of the transition to adult care matter most and to describe the current care gap as experienced by European caregivers to inform the guideline scope.

**Methods**: An international web-based survey was conducted by ERN-ITHACA in January-February 2023. Priorities for a good transition process and current care gaps in Europe were identified using the 'Mind the Gap'-scale. The surveys were created in plain and Easy-to-Read language and available in nine European languages.

**Results**: 157 caregivers from 15 European countries completed the survey, representing over 40 conditions, including the Phelan-McDermid, Rubinstein-Taybi, 22q11.2 deletion, and Kleefstra syndromes. Care gaps were identified, particularly related to process issues such as the preparation for and adaptation to adult healthcare, supporting independence, and planning for the future. Items considered essential for optimal healthcare were related to individualised approaches, information provision, and coordination of care.

**Discussion**: Coordinated, specialised, individualised, and multidisciplinary care is required to support youth with rare conditions and intellectual disability in the transitional age. Supporting young people's independence, orchestrating multidisciplinary care, and ensuring effective communication are particularly challenging in the transition to adult healthcare for this population.



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## ID 61 POSTER PRESENTATION

### Environmental enrichment for children with developmental disabilities and behavioral phenotypes: bridge from theory into practice.... yes we can!

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**Background:** Having the experience of working in the daily reality at the Center for Developmental Disorders at the University Hospitals Leuven and being aware of the concept of brain plasticity and effects of environmental enrichment, the idea grew of an innovative and inclusive childcare concept.
The mission of family-centered inclusive nursery Villa Clementina- founded 2014 - is that childcare should be a possibility for every child regardless the socio-economical background or medical problems. Also severely disabled and autistic children are welcome.

**Methods:** Villa Clementina every day welcomes 33 children (aged 0-6 years) of whom 1/3 of the children have special and multiple needs. A multidisciplinary framework (pediatrician, clinical pedagogue, physiotherapist, speech therapist, nurse and child caretakers) takes care with the help of volunteers. Education is integrated for school-aged children.

**Results:** In an 11-year period, more than 300 children have been taken care of, of whom 1/3 with (multiple) needs having a variety of genetic syndromes. Experience learns that children followed developmental trajectories, often different and more challenging than expected by caregivers. Even the most disabled and autistic children learned to perform in a mixed group, with positive effects on alertness, development, wellbeing and coping.
We focus on two boys with Smith Magenis Syndrome (17911.2 deletion) who left the nursery with a mean IQ and low-average verbal skills. Their challenging behavior in the nursery was less pronounced than in their home environment

**Conclusion:** A thorough inclusive childcare setting can provide a context for environmental enrichment in a critical window for learning and thus harness neuroplasticity and influence behavioral phenotypes. Further research on the effects of exposure to a rich environment with multiple - and not always predictable- stimuli versus a more tranquil and structured environment is planned e.g. impact on alertness, wellbeing and coping.

**Keywords**: Smith magenis syndrome, brain plasticity, environmental enrichment, inclusion, behavioural phenotype

## ID 62 POSTER PRESENTATION

### Establishing a multidisciplinary clinic for children with Smith Magenis Syndrome: the Leuven experience

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**Background:** Individuals with Smith-Magenis syndrome (SMS) present with complex physical, behavioral, and cognitive challenges throughout the lifespan. Medical monitoring of syndrome-related physical symptoms including myopia, sensorineural hearing loss, scoliosis, and abnormal sleep patterns is necessary, as well as coordinated behavioral interventions and a systematic approach to psychotropic medication management due to the severe behavioural challenges in SMS, such as agitation, self-injury and aggression.

**Method:** Based on both professional interest and patient need, in 2021 a collaboration was set up between the Centre for Developmental Disabilities and the Centre for Human Genetics at UZ Leuven in order to create a multidisciplinary clinic/care path for this population.

**Results:** The SMS clinic @UZ Leuven formally started in the summer of 2022. The multidisciplinary clinical team includes a neurodevelopmental pediatrician, clinical (educational) psychologists, clinical geneticist and child psychiatrist. In order to standardize care, a comprehensive literature review was done to identify best practices for the ongoing medical management and support of individuals with SMS. To date, eleven patients with Smith-Magenis syndrome have been served with additional phone consultations for individuals unable to attend clinic. A medical management checklist is used, medication management including genetic testing is available, and behavioral management including self-injury, toilet-training and feeding challenges as well as sleep management are also discussed. Parents are linked to resources for education, support and recreation. Letters summarizing each visit are sent to the providers who referred each patient and orders are written by prescription or within local health systems for labs and tests and referral for specialty care for problems identified at the visit can be ordered.

**Conclusion:** Comprehensive and integrated care for this population extends outside the medical clinic to the home, the special education classroom, and the community, and requires multidisciplinary collaboration.



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## ID 65 POSTER PRESENTATION

### Blood Biomarkers for Neurodegeneration and Alzheimer's Disease in Individuals with Intellectual Disabilities: A Systematic Review

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**Introduction**: Individuals with intellectual disability (ID), particularly those with Down syndrome (DS), are at a markedly increased risk of developing Alzheimer's disease (AD) and related neurodegenerative disorders. This elevated risk is partly attributable to genetic factors, such as the triplication of the APP gene in DS, as well as other, less well-understood mechanisms in non-DS ID populations. Early detection of AD in individuals with ID is particularly challenging due to the level of intellectual disability, atypical symptom presentation, and frequent comorbidities. Blood-based biomarkers for AD and neurodegeneration, such as amyloid beta (Aβ), tau, neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP), and have shown great promise in the general population, but their utility in ID remains unclear.

**Methods**: A systematic literature search was conducted across MEDLINE, Embase, and the Cochrane Library using MeSH terms and relevant keywords. A total of 2,453 records were identified, of which 88 studies were included in the final review. Methodological quality was assessed, and a narrative synthesis was performed due to expected heterogeneity in study designs and outcomes. Studies focusing on AD screening and diagnostic applications in DS were examined through targeted subanalysis to assess biomarker performance and clinical relevance.

**Results**: Most studies focused on DS, with limited evidence in other ID forms. Investigated biomarkers included Aβ40, Aβ42, phosphorylated tau (pTau), total tau (tTau), NfL, and GFAP. Preliminary evidence suggests that NfL consistently correlated with disease severity and progression but lacked AD specificity. pTau, particularly pTau181, appeared most promising for AD diagnosis in DS, outperforming tTau though data remain sparse. GFAP may provide complementary information, rising later than NfL but with lower diagnostic accuracy. The Aβ42/40 ratio was informative for pathophysiology but inconsistent for case-level diagnosis.

**Discussion/Conclusion**: Preliminary evidence suggests NfL and pTau181, possibly combined with GFAP, offer greatest potential for early detection and monitoring of AD in DS. More longitudinal, standardised, and multi-condition studies are needed to confirm biomarker validity across ID populations.

**Keywords**: Intellectual disability; Down syndrome; Alzheimer's disease; Blood-based biomarkers; Neurodegeneration



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## ID 67 POSTER PRESENTATION

### The need for interprofessional collaboration in the care of individuals with rare genetic intellectual disability: A patient journey mapping study (Project 1)

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**Introduction**: People with rare genetic intellectual disability syndromes (RGIDS) have physical and mental health related problems, with a high risk for challenging behavior (e.g. aggression, self-injury). Their care requires long-term complex care involving multiple healthcare professionals. Parents play a key role in coordinating and interacting with these professionals. This study aimed to explore parents' journey with the healthcare system, the networks they have built, and their perceptions of interactions with healthcare professionals over time.

**Methods:** A qualitative approach was used, interviewing parents of people with RGIDS and challenging behavior. All interviews were audio-recorded, transcribed verbatim and analyzed using thematic analysis. Data was collected until sufficiency was reached. Findings were visualized using Patient Journey Mapping.

**Results**: Among the 13 parents interviewed, most described their journey as beginning with concerns about their child's early development. When voicing these concerns, some parents felt unheard by their general practitioner or pediatrician. For some, obtaining specialized care and ultimately receiving a diagnosis was only made possible through their own persistence—navigating a journey filled with referrals, extensive testing, diagnoses, and well-intentioned yet often ill-suited advice on challenging behaviors that did not align with daily life.
In terms of their care network, physicians from the medical domain dominated the journey, while behavioral specialists and psychiatrists were rarely involved. This added to parents' ongoing uncertainty and frustration, as their child's challenging behaviours remained unaddressed and impacting their daily life. Also, the lack of interprofessional coordination led to parents' wish for a single point of contact and coordination of proper care.

**Discussions/Conclusions:** Due to a lack of guidance, people with RGIDS were rarely seen by behavioral professionals or psychiatrists, despite numerous consults with medical healthcare professionals. Parents were left to lead the care process themselves, with much of the focus placed on physical problems. This highlights the need for better collaboration and coordination between medical and behavioral professionals to ensure high quality, person-centered care.

**Keywords:** Rare genetic intellectual disability syndrome, Challenging behavior, Parents, Journey



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## ID 68 POSTER PRESENTATION

### Who Takes the Lead? Dispersed Responsibility in Interprofessional Collaboration around Challenging Behaviour in Rare Genetic Intellectual Disability Syndromes (Project 2)

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**Introduction**: People with rare genetic intellectual disability syndromes (RGIDS) have physical and mental challenges, and are at high risk for challenging behaviour (e.g. aggression, self-injury). Managing these behaviours requires integrated care from multiple medical and behavioural professionals. Parents frequently experience gaps in behavioural support and assume expert roles beyond their capabilities. This study explored the barriers and facilitators in interprofessional collaboration for managing challenging behaviour in people with RGIDS, with parents in an expert role.

**Methods**: A qualitative approach was used, interviewing parents and healthcare professionals of people with RGIDS and challenging behaviour. All interviews were audio-recorded, transcribed verbatim and analysed using the thematic analyses. Data was collected until sufficiency was reached.

**Results**: Interprofessional collaboration was most effective when the experiential knowledge of parents was explicitly acknowledged and integrated into shared decision-making. Mutual trust and equal partnership served as essential preconditions. At the same time, structural and organizational barriers - such as fragmented care, separated funding, and non-integrated information systems - limited the potential for cross-organizational collaboration. Healthcare professionals reported feelings of powerlessness, while parents were often hesitant toward interventions addressing challenging behaviour. Due to the lack of structural support, the coordination of collaboration frequently depended on individual professionals, who did not always feel responsible or sufficiently competent to take the initiative.

**Discussions/conclusions**: Interprofessional collaboration around challenging behaviour in people with RGIDS is complex and shaped by factors operating at multiple levels. While structural barriers call for system-level interventions, immediate opportunities for improvement lie within professional practice. When professionals take responsibility for actively initiating collaboration and explicitly involve parents as equal parents and experts, the quality of shared decision-making improves. Future research should focus on the intentions, attitudes, and competencies of healthcare professionals regarding interprofessional collaboration and learning, as these factors may provide more immediate opportunities to enhance care for people with RIGDS.

**Keywords:** Rare genetic intellectual disability syndrome, Challenging behaviour, Parents, Healthcare professionals, Interprofessional collaboration



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## ID 69 POSTER PRESENTATION

### Healthcare professionals' intentions and competencies towards interprofessional collaboration around challenging behaviour in people with rare genetic intellectual disabilities syndromes (Project 3)

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**Introduction**: Interprofessional collaboration (IP) is crucial for guidance, care and therapeutic interventions for people with rare genetic intellectual disability syndromes (RGIDS). Especially for those who are at high risk for challenging behaviour (e.g. aggression, self-injury) who require the expertise of multiple medical and non-medical specialists, from multiple care domains. Unfortunately, in practice, achieving effective IP often proves challenging. Healthcare professionals report to face systemic, organizational, interpersonal, and individual barriers. While systemic and organizational barriers are often beyond the control of individual professionals, they do have control over their own behaviour regarding IP. To date, little is known about healthcare professionals' intentions and competencies in this context. Drawing on the Integrated Behaviour Model and the Canadian Interprofessional Health Collaborative (CIHC) framework, this study explores healthcare professionals' intentions and competencies to collaborate effectively in the complex care around challenging behaviour for people with RGIDS.

**Methods:** This cross-sectional study administered 4 questionnaires to medical and non-medical specialists (medical doctors, psychiatrists, healthcare and educational psychologists, psychiatrists working in hospitals, intellectual disability care, and mental healthcare settings). The *Interprofessional Collaborative Competency Attainment Survey (ICCAS)* and *Chiba Interprofessional Competency Scale (CICS29)* were administered in full, collectively covering all CIHC competency domains (role clarification, interprofessional conflict resolution, team functioning, collaborative leadership, interprofessional communication, patient centered care). The *Interprofessional Collaboration Competency Scale for Children with Medical Complexity (ICC-CMC)* was used to assess competencies related to complex care coordination. The *Interprofessional Attitudes Scale (IPAS) and Index for Interdisciplinary Collaboration (IIC)* measured healthcare professionals' intentions toward interprofessional collaboration. Descriptive analyses will be conducted for all measures.

**Results**: The results will uncover healthcare professionals' self-assessed competencies and intentions to collaborate interprofessionally and across care domains for people with RGIDS and challenging behaviour. Descriptive statistics will be presented for each CIHC domain measured by ICCAS and CICS29. ICC-CMC scores will provide insight into competencies specific to complex care coordination for children with medical needs, while IPAS and IIC scores will capture healthcare professionals' collaborative intentions. Data collection is ongoing, with results anticipated in April 2026.

**Discussions/conclusion**: Gaining insight in healthcare professionals' intentions and competencies, helps to identify opportunities for improving IP in the context of guidance, care and therapeutic interventions for people with rare genetic intellectual disability syndromes (RGIDS). This study is one of three interrelated studies within a larger research project on IP. Combined with findings from our earlier studies exploring parents' journey and experiences with interprofessional collaboration (Project 1 and 2), this study provides interesting new knowledge and information for valuable discussion on shaping care for people with RGIDS and challenging behaviour. Presenting these findings at the EuroNDD conference offers a valuable opportunity to validate and enrich our conclusions through discussion with an international community of experts, ensuring their global relevance and applicability.

**Keywords**: Rare Genetic Intellectual Disability Syndromes, Challenging Behaviour, Interprofessional collaboration, Interprofessional Competencies



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## ID 70 POSTER PRESENTATION

### A therapeutic education program for patients with PIMD/polyhandicap in France: a multidisciplinary and network-based approach.

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**Introduction**: In recent years, the French Polyhandicap/PIMD Reference Center for Rare Diseases has developed a therapeutic education program for children with polyhandicap/PIMD and their parents, which includes a nutrition module that is the result of a collaboration between the four centers of the network.

**Methods:** The program was developed by teams of doctors and paramedics working with partner families. The teams worked on five workshops to ensure optimal care for these patients in relation to the nutrition module. An initial shared educational assessment is used to guide families towards topics tailored to their children's needs. The workshops were developed by teams of identified professionals and experts on the subject and are then made available to everyone.

**Results:** The workshop on oral health aims to highlight the importance of tooth brushing and the different techniques available. The workshop on the three dimensions of eating examines nutrition with the adaptation of food intake, safety with the positioning of the young person, and the texture of food to ensure the notion of pleasure. Two workshops are dedicated to nasogastric tubes and gastrostomy tubes in order to work on families' perceptions of these devices and their everyday use. A workshop on constipation explores its causes, consequences, and treatments.

**Discussion/Conclusion:** The participation of peer caregivers allows for a relevant approach to the psychosocial repercussions that cut across the various themes.
This project demonstrates that inter-university hospital collaboration, led by paramedical teams supported by doctors and accompanied by caregivers, is not only possible but also extremely fruitful for the creation of a therapeutic education program that closely meets the needs of patients with Polyhandicap/PIMD and their families. It aims to be developed into routine care provided by any pediatric team treating these patients.

**Key words:** Polyhandicap/PIMD, therapeutic education, caregiver, nutrition



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## ID 72 POSTER PRESENTATION

### Health and care characteristics of aging adults with Profound Intellectual and Multiple Disabilities: a cross-sectional study in a national cohort

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**Introduction:** Life expectancy in individuals with Profound Intellectual and Multiple Disabilities/Polyhandicap (PIMD/PLH) have increased making informations essential for age-appropriate care planning. This study compares health characteristics and healthcare consomption between younger and older adults with PIMD/PLH.

**Methods:** This cross-sectional study used data from the French cohort of individuals with PIMD/PLH. Inclusion criteria: (i) age > 3 years ; (ii) a diagnosis of polyhandicap (early brain lesion causing a combination of severe motor impairment, profound intellectual disability, high dependency). Data included 1) health characteristics, health care consumption, vital status. Comparisons were made between two adult groups ≤ 45 vs. > 45 years. Results. Older adults showed greater severe dependency while overall severity was similar between age groups. Comorbidity profiles differed between age groups. Older aldults received less medical and paramedical care.

**Discussion/conclusions:** This study advocates for a lifespan-medical and reeducative care for individuals with PIMD/PLH.

**Key word:** Polyhandicap; Profound Multiple Intellectual Disabilities; aging; health characteristics; care consumption.

## ID 73 POSTER PRESENTATION

### Factors Associated with the Quality of Life of Parents of Individuals with Profound Intellectual and Multiple Disabilities/Polyhandicap: A 5-Year Follow-Up

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**Introduction:** Compared with French population norms, parents of individuals with profound intellectual and multiple disabilities report lower quality of life levels across the physical, psychological, and social domains. In a previous cross-sectional study, we showed that the main determinants of their quality of life were related to their own health status, financial situation, and coping strategies used to face a difficult life event. The aim of the present study was to examine factors associated with changes in parental quality of life over time.

**Methods:** This study was conducted within the French national EVAL-PLH cohort. Parents' quality of life was assessed using the WHOQOL questionnaire at two different time points, five years apart (2015 and 2020). For each dimension, parents were classified into two groups: deteriorated and non-deteriorated quality of life.

**Results:** One hundred parents completed the questionnaires at both time points. Physical quality of life was more often deteriorated when the patient's condition was impaired according to respiratory or urinary scores, and when medication burden or the number of medical devices was higher. Psychological deterioration was associated with the parent's own emotional decline but was not related to patient characteristics. Social deterioration was linked to parental sleep disturbance. Parents of children living in medico-social institutions reported more deteriorated quality of life levels than those whose children were followed in rehabilitation units (SSR).

**Conclusion:** Identifying the most vulnerable parents is crucial for healthcare teams to enable tailored monitoring and preventive support.

**Key words:** polyhandicap, parents, quality of life

## ID 74 POSTER PRESENTATION

### Social representations and parenthood: a qualitative study among parents of persons living with Profound Intellectual and Multiple Disabilities/Polyhandicap

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**Introduction**: People with Profound Intellectual and Multiple Disabilities (PIMD)/Polyhandicap require ongoing support in all aspects of their lives. Parents of these individuals provide at least part of this support. Several studies have highlighted the physical, psychological, social, temporal, and economic implications of this support (e.g., Geuze et al., 2023).

To our knowledge, no study has explored the meaning of parenthood per se and the practical and identity implications of these representations in the French context. Our objective was therefore to explore the social representations associated with parenthood among parents of people with with PIMD/Polyhandicap through the accounts of their lived experiences (Jodelet, 2006).

**Methods**: Interviews were conducted by telephone or videoconference with thirty-four parents. These interviews were analysed thematically (Braun & Clarke, 2021).

**Results**: Five themes were developed: (1) Ensuring a good life for one's child: a parental responsibility; (2) Ensuring your child's well-being: the expertise of the parent-carer-educator; (3) Putting your child first... until you can't anymore; (4) Sharing and connecting: recognising and understanding each other, loving each other, and being together; (5) A-typical parenthood: exclusion and reappropriation of normality.

**Discussion/Conclusion**: Our findings highlighted representations associated with a normalised view on parenthood, on the basis of which parents have internalised a certain parental identity (Duveen, 2001). The meanings attributed to parenthood reflect the ideologies that underpin them: intimate responsibilities, intensive parenting/mothering (Riley et al., 2018), and ableism. However, these systems of power and inequality that permeate and underpin parenting in the context of PIMD/Polyhandicap reinforce gender roles and essentialising maternal care while being simultaneously challenged by the participants. Thus, while representations of parenthood contribute to the social health inequalities impacting parents of people with PIMD/Polyhandicap, they can also be deployed to develop self-confidence and positive social identities.

**Key words:** Parenthood; Social representations; Profound Intellectual and Multiple Disabilities; Polyhandicap.

## ID 75 POSTER PRESENTATION

### Impact of Communication and Feeding Disorders on the Quality of Life of Patients with Polyhandicap

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**Introduction:** Polyhandicap (PLH) is a severe and complex condition combining profound intellectual impairment and severe motor disability. Patients with PLH often present with communication disorders (oral and non-verbal) and feeding difficulties that can affect their quality of life. Assessing the impact of these disorders on quality of life is essential, as it helps guide interventions such as speech and language therapy, which aims to improve communication and support patients with feeding difficulties. The objective of this study was to determine which disorders appear to impact, according to caregivers (health professionals and families), the quality of life of these patients.

**Materials and Methods:** Data for this study were drawn from the cohort of patients with polyhandicap (EVAL-PLH). Quality of life was assessed using the PolyQoL questionnaire, validated according to current standards, and completed by both the primary caregiver and a family member. These data were then analyzed in relation to variables concerning communication (oral language, non-verbal communication) and feeding (swallowing disorders, aspiration, feeding mode, gastroesophageal reflux, drooling).

**Results:** Communication was significantly associated with better social and overall quality of life according to both caregivers and families: the more communication abilities were preserved, the higher the perceived quality of life. Feeding disorders showed more mixed results. Feeding mode was associated with quality of life across all dimensions for families, and only with the social dimension for caregivers: more autonomous feeding was linked to better quality of life. Gastroesophageal reflux was associated with poorer social quality of life according to caregivers. Drooling and swallowing disorders had no significant effect on quality of life.

**Conclusion and Discussion:** Communication and feeding disorders significantly influence the quality of life of patients with polyhandicap, although perceptions differ between caregivers and families. Speech and language therapy, addressing both domains, could play a preventive and supportive role by guiding families and caregivers in managing these difficulties, thereby contributing to improved overall quality of life.

**Keywords:** Polyhandicap, Quality of life, Communication and feeding disorders



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## ID 76 POSTER PRESENTATION

### Factors Associated with Family Functioning Among Parents and Siblings of persons with PIMD/Polyhandicap

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**Introduction:** Families of individuals with Profound Intellectual and Multiple Disabilities/Polyhandicap (PIMD/Polyhandicap) face unique and enduring challenges that can significantly impact family functioning. The complex care needs, emotional burden, and social implications associated with PIMD/Polyhandicap often reshape family dynamics, roles, and daily routines. Understanding how these families adapt, function, and maintain cohesion over time is essential for developing effective support systems. This study aims to identify the specific factors that influence family functioning in order to help to better support these families and improve their quality of life.

**Methods:** This study was included in the French national polyhandicap cohort (EVAL-PLH) carryed out in 4 specialized rehabilitation centers and 9 residential facility structures. Three different populations were eligible: i. persons with severe PIMD/Polyhandicap; ii. familial caregivers of the included persons; and iii. institutional caregivers of the included persons. Data were collected from self-reported questionnaires fullfilled by parents. The data collected included: sociodemographics, health status, social participation and psychocomportemental aspects (coping), parents' satisfaction regarding their interactions with healthcare teams, as well as questions addressing the emotional, relational, and professional difficulties of the siblings. QoL was assessed using WHOQOL-BREF and the familial functioning was assessed with the FAD short form.

**Results:** We collected questionnaires from 202 parents, 60% women and 40% men. Factors associated with better family functioning among parents included a higher quality of life score, the absence of perceived rejection from family members or society, participation in family celebrations, and the use of positive coping strategies. Among siblings, better family functioning was associated with fewer difficulties in their emotional, social, and professional lives, as well as fewer psychological support needs. Family functioning was not found to be related to the parents' health status or their interactions with healthcare teams.

**Discussion/Conclusion:** Our findings highlight the importance of psychosocial and relational factors in family functioning. Better quality of life, social inclusion, family participation, and positive coping strategies were linked to stronger family dynamics for parents. Conversely, family functioning appeared independent of parents' health status or interactions with healthcare teams. These results suggest that promoting social support and adaptive coping may strengthen family resilience, regardless of health-related challenges.

**Key words:** PIMD/Polyhandicap ; parents ; siblings ; familial functioning



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## ID 77 POSTER PRESENTATION

### Thyroid Hormone Transporter Monocarboxylate Transporter 8 (MCT8) Deficiency : A Case Report

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**Introduction:** MCT8 deficiency, also known as Allan-Herndon-Dudley syndrome is a rare neurodevelopmental disease caused by mutations in the SLC16A2 gene which encodes the thyroid hormone transmembrane transporter monocarboxylate tranporter 8.(1) The resulting disordered thyroid hormone transport results in a clinical picture of intellectual and motor disability due to cerebral hypothyroidism and chronic peripheral thyrotoxiocosis. (2)

In this case report we aim to describe case presentation, diagnosis and management of MCT8 deficiency in an 18 month old boy.

**Methods:** Review of patient records and published literature on MCT8 deficiency.

**Results:** This case presented to a neurodevelopmental clinic at 14 months with a history of delayed motor milestones and central hypotonia. Initial examination findings included significant central hypotonia, right sided hypertonia and brisk reflexes. He was born at term following an uncomplicated pregnancy. There was no history of developmental or motor disorders in the family.

An MRI Brain was performed and demonstrated delayed myelination. Biochemical investigations including thyroid function tests were undertaken and demonstrated a low T4 level 10.8pmol/L (RR 11-21), mildly raised TSH 5.45mU/L (RR 0.1-4.8) and raised serum T3 7.6pmol/L (RR2.6-6.0). Genetic testing confirmed MCT8 deficiency and he was commenced on Tiratricol (Triac) treatment with close endocrine and neurodevelopmental follow up.

**Discussion:** MCT8 deficiency is a genetic disorder characterized by a clinical spectrum of severe intellectual and motor disability due to cerebral hypothyroidism with peripheral symptoms of thyrotoxicosis. It occurs due to a defect in the thyroid hormone transporter monocarboxylate transporter 8 (MCT8).

MCT8 plays a crucial role in the transport of thyroid hormone across the blood-brain barrier. (3) It has a characteristic thyroid profile with elevated plasma T3 levels, low T4 levels and normal or slightly elevated TSH with a high T3:T4 ratio. (1)

Aim of treatment is to improve neurocognitive phenotype while managing peripheral thyrotoxicosis. The thyroid hormone analogue Triac can be used to reduce the peripheral thyrotoxicosis in patients and may improve the neurocognitive phenotype when treatment is initiated early in life.

**Conclusions:** MCT8 deficiency is a rare cause of X linked neuro-developmental delay with characteristic clinical and biochemical findings. There are potential treatment options which may improve outcomes if commenced early in life. This case highlights the importance of performing thyroid function tests as part of initial diagnostic work up in children with abnormal neurodevelopment.

**Key words:** MCT8 deficiency, Allan-Herndon-Dudley syndrome, case report, thyroid hormone transporter, cerebral hypothyroidism

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## ID 78 POSTER PRESENTATION

### Exploring values in healthcare decision-making for individuals with rare genetic neurodevelopmental disorders and their caregivers: a scoping review and qualitative study

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**Introduction:** Rare genetic neurodevelopmental disorders (RGNDs) associated with intellectual disabilities (ID) often involve multi-organ comorbidity and lifelong care needs. Developing clinical practice guidelines for this population demands alignment with the values of individuals, their families, and caregivers to ensure care that is both effective and person-centered.

**Methods:** We conducted a scoping review and qualitative research to explore healthcare-related values of individuals with RGNDs and their families/caregivers. A systematic search of MEDLINE, Embase, PsycINFO, and CINAHL identified 125 relevant qualitative studies, which were analyzed using content analysis. In addition, semi-structured interviews with 18 parents of individuals with 15 different (ultra)rare conditions were thematically analyzed.

**Results:** Content analysis revealed several key values, including autonomy, person-centeredness, feasibility, competence of and connection with the healthcare professional, and the accessibility, coordination, and stigma-free nature of healthcare. Key decision-making considerations included balancing benefits and harms on both individual and family levels, dealing with uncertainty, prioritizing health issues, and addressing identity-related concerns. Parent interviews highlighted two central themes: proportionality (balancing potential harm versus treatment necessity and feasibility) and equality (ensuring inclusivity, accessibility, and continuity of care). Healthcare decision-making was viewed as a collaborative process, with strong emphasis on parental involvement and respect for the autonomy of the individual.

**Conclusion:** When developing clinical practice guidelines, developers should consider values such as proportionality and equality and pay particular attention to family-level impacts and identity-related concerns. Incorporating these values into guidelines and fostering open discussions during consultations can lead to more personalized care that reflects the priorities of individuals and their families/caregivers. Further research is needed, particularly to include the perspectives of individuals with intellectual disabilities themselves.

**Key words**: healthcare, decision-making, intellectual disabilities, rare conditions, values, clinical practice guidelines



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## ID 79 POSTER PRESENTATION

### Clinical practice guideline development for rare genetic conditions associated with ID: the ERN-ITHACA experience

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**Introduction:** Rare genetic conditions associated with intellectual disabilities (ID) significantly affect both physical and psychosocial functioning, often requiring lifelong, multidisciplinary care. Due to their complexity and rarity, providing optimal care can be challenging for healthcare professionals. Clinical practice guidelines (CPGs) offer evidence-based recommendations to support diagnosis and management, but the development of such guidelines for rare conditions is hindered by the limited scientific evidence available**.**

**Methods**: With European Reference Network (ERN) ITHACA, the European network on rare malformation syndromes and rare intellectual disabilities, we develop clinical practice guidelines for various genetic syndromes and shared health problems. In parallel, we conduct research to refine guideline methodology for rare disorders, including collaborative priority-setting for topics and the integration of the values of individuals and families.
Results: ERN-ITHACA has convened expert groups to develop guidelines for rare genetic conditions associated with intellectual disabilities. New guidelines, including those addressing the transition to adult healthcare and Kleefstra syndrome, are set to be published this winter. This presentation will detail the guideline development process, highlighting challenges and solutions specific to rare genetic conditions and intellectual disabilities, with practical examples from ERN-ITHACA guidelines

**Conclusion:** The development of clinical practice guidelines is essential for providing evidence-based care and improving health outcomes for individuals with rare intellectual disabilities. By offering a structured framework for high-quality care, these guidelines have the potential to promote health equity across Europe. This presentation aims to inform and inspire healthcare professionals, researchers, and patient partners involved in the development or implementation of clinical practice guidelines.

**Key words:** clinical practice guidelines, evidence-based medicine, methodology, genetic syndromes, rare disease, intellectual disabilities



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## ID 80 POSTER PRESENTATION

### The *ProMiSe* of integrating knowledge and tailored intervention strategies to improve NDD care

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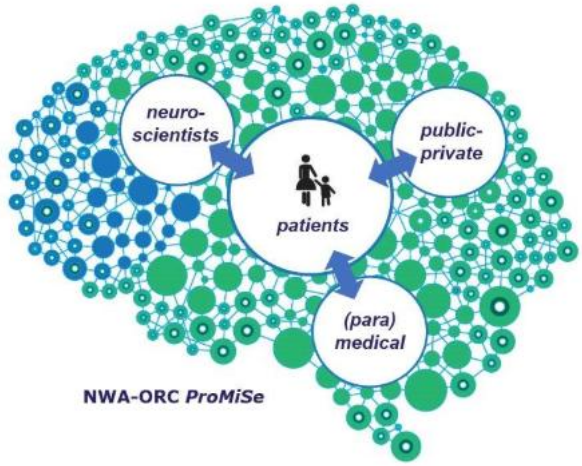


Neurodevelopmental disorders (NDDs) comprise a heterogeneous group of disorders with a large social impact. Frequently, similar genes appear affected by rare variants across NDDs and psychiatric conditions. The steep increase in gene discovery in these so-called Mendelian syndromes, syndromes caused by rare monogenic variants, allows us to study underlying neurodevelopmental biology and detailed clinical phenotyping. With the multidisciplinary ProMiSe project, hand in hand with several public private parties, the researchers intend to make a blueprint for how the integration of neurobiological and clinical knowledge can lead to improvement of care for such patients. Another important aspect of the project is mapping all existing knowledge about rare genetic syndromes and possible interventions. Knowledge from multiple expertises such as developmental biology, neuropsychology, psychiatry and genetics will be combined and made directly available for patients and their families. The implementation of tailored intervention(s) for rare NDDs is the highly mandatory next step that should be taken after genetic diagnosis. We thereby investigate the consequences of a known genetic deviation on neurobiology, neurocognition and behavior (bottom-up) rather than investigate heterogeneous groups on certain neurobiological aspects (top-down). This allows us to investigate the possibility of therapeutic (early/preventive) interventions and subsequent improvement of care. We aim to enhance the development and implementation of such novel intervention strategies for NDDs by obtaining fundamental insights in both the clinical, psychological and biological consequences of mutated genes that cause certain NDDs (eg WitKoS, KBG). To unravel the biological framework behind these causative genes we use a battery of functional assays (including human brain organoids) to define developmental time windows in which the intended intervention would be most effective as well as neurocognitive data and neuropsychiatric assessments. By achieving this, we also aim to provide the field with a template on how to integrate fundamental insights in biological mechanisms, with cognitive and psychiatric profiling in distinct syndromes. In this way tailored intervention strategies targeted at severe behavior and psychiatric problems that are frequently encountered can be developed.

**Key words: i**ntervention strategies, neurodevelopmental disorder, developmental neurobiology, neuropsychology, psychiatry and genetics



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## ID 81 POSTER PRESENTATION

### From building an International and Interdisciplinary Network towards Care Principles for Individualized, Interdisciplinary, and Holistic Care for Individuals with PIMD/polyhandicap

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**Introduction:** Individuals with profound intellectual and multiple disabilities (PIMD)/polyhandicap experience severe intellectual impairments, significant motor challenges, and additional sensory and health issues. Despite the heterogeneity within this group, all individuals are highly and lifelong dependent on care and support from others for their quality of life. The absence of Clinical Practice Guidelines (CPGs) for this population hinders the provision of adequate, evidence-based care and support. To address this gap, an international collaborative initiative was launched to develop CPGs specifically for individuals with PIMD/polyhandicap.

**Methods:** During the period 2020-2025 an international, interdisciplinary consortium (n=41) was formed through the European Reference Network (ERN)-ITHACA, comprising experts from 14 European countries (Belgium: 2; Bulgaria: 1; Denmark: 2; France: 9; Germany: 1; Italy: 1; Luxembourg: 1; Netherlands: 17; Norway: 1; Poland: 2; Romania: 1; Spain: 1; UK: 2), including family members with lived experience. Workgroups within the consortium worked in parallel with the guideline development process. Topics such as motor functioning, sleep, pain, and behavior were prioritized based on their relevance, urgency, and interdependence. The CPGs were developed using a systematic literature review based on the PRISMA methodology, expert consultations (including family members with lived experience), a hybrid consensus meeting, a written voting procedure, and external peer reviews. Additionally, a thematic analysis of the evidence tables was conducted and discussed within the consortium to define care principles for individualized, interdisciplinary, and holistic care for individuals with PIMD/polyhandicap.

**Results:** Three guidelines were developed, addressing assessment procedures and interventions for motor functioning, sleep, and pain. Based on these recommendations, care principles for individualized, interdisciplinary, and holistic care for individuals with PIMD/polyhandicap were established to guide both the care of individuals and support for their families.

**Conclusions:** This study discusses the process of creating an international, interdisciplinary consortium of family members and clinical and scientific experts, initiated under the framework of ERN-ITHACA. It also presents recommendations for assessment procedures and interventions regarding motor functioning, sleep, and pain, which together underpin a set of care principles for individuals with PIMD/polyhandicap, emphasizing the need for individualized, interdisciplinary, and holistic care.

**Key words:** Profound intellectual and multiple disabilities; clinical practice guidelines ; care principles for individualized, interdisciplinary, and holistic care.

## ID 82 POSTER PRESENTATION

### Lessons Learned from the Development of Clinical Practice Guidelines for Individuals with PIMD/polyhandicap: Methodological Challenges and Future Directions

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**Introduction:** The shift toward evidence-based care and support for individuals with profound intellectual and multiple disabilities (PIMD)/polyhandicap is accelerating, with the development of Clinical Practice Guidelines (CPGs) playing a central role. CPGs provide recommendations designed to optimize patient care, enhance healthcare quality, reduce unwarranted practice variation, and facilitate the translation of scientific evidence into clinical practice. An international interdisciplinary expert group from 14 European countries developed CPGs to optimize care for individuals with PIMD/polyhandicap. The process of developing evidence-based recommendations typically involved three steps: 1) synthesizing the best available scientific evidence including evaluating the benefits and risks of alternative care options, 2) integrating expert experience, and 3) considering patient perspectives. The aim of the current study is to reflect on these steps in the development of CPGs specifically for individuals with PIMD/polyhandicap, discuss the challenges encountered, and propose directions for future interdisciplinary research and guideline development.

**Methods:** An international and interdisciplinary consortium of 41 experts from 14 European countries was established under the European Reference Network (ERN)-ITHACA. The consortium comprised family members with lived experience and clinical and scientific experts, who collaborated in parallel with the guideline development process, participating in approximately 50 meetings. The CPGs with recommendations were developed through a standardized ERN-ITHACA procedure, starting from a systematic literature review conducted according to the PRISMA methodology, followed by online workgroup meetings, a hybrid consensus meeting, a written voting round, and external peer reviews.

**Results:** We identified methodological challenges and limitations across all phases of the process, including issues related to terminology, search strategies, and the need for interdisciplinary expertise in the selection and appraisal of literature. All recommendations were of (very) low levels of evidence, primarily due to the characteristics of the population and the limited availability of scientific literature. We discussed the implications of these challenges for identifying knowledge and care gaps and underscored the need for high-quality research to address these gaps in the future.

**Conclusions:** There is a need for: 1 tailored CPG methodologies for individuals with PIMD/polyhandicap, 2) a shared conceptual framework addressing the needs of individuals with PIMD/polyhandicap and their families, and 3) guidance on implementing these recommendations within an individualized, interdisciplinary, and holistic care approach. To meet these needs, we advocate for: 1) empowering parents and caregivers in assessment and evaluation (e.g., caregiver assessment tools, GAS, GAF), 2) enhanced care coordination, 3) the establishment of an international cohort and registry, 4) single-subject study designs, and 5) replication of assessment studies.

**Key words:** Profound intellectual and multiple disabilities; clinical practice guidelines ; methodology ; interdisciplinary care.



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## Meet our presentors

**Akçahan Akalın** is a pediatric geneticist and PhD candidate in Medical Genetics at Hacettepe University, Türkiye. She currently works at Diyarbakır Children's Hospital and has a special interest in neurodevelopmental disorders, rare genetic diseases, and genotype–phenotype correlations in consanguineous populations. Her research focuses on whole genome sequencing, copy number variation analysis, and undiagnosed neurogenetic and syndromic conditions. She has authored several peer-reviewed publications and actively participates in international genetics and dysmorphology meetings.

**Marie-Anastasie** is an Associate Professor in Social and Health Psychology at the Jean-François Champollion University Institute, France. She is a member of the Centre de Recherches Sciences Sociales Sports et Corps (Center for Social Science Research on Sport and the Body), Toulouse University, France. She is also part of the Polyhandicap French Research NEtwork. Drawing on critical health psychology approaches, her work focuses on life habits, lived experiences, and knowledge associated with chronic conditions, such as polyhandicap/PIMD.

**Yaqoub Ashhab** is an associate professor of genomics and bioinformatics at Palestine Polytechnic University. His research focuses on applying genomics and multi-omics approaches to understand human diseases, particularly cancer and immune-related disorders. He holds a PhD in molecular immunology and conducted postdoctoral research in cancer biology, including the identification of the cancer biomarker BIRC7. He actively collaborates with European research networks and is committed to capacity building in genomic research in developing countries.

**Kristin A Bakke** is trained as a pediatrician and is currently employed at the Norwegian Centre for Rare Diseases, where her work focuses on neurodevelopmental disorders, including autism and intellectual disability in individuals with genetic syndromes. Her interest in autism developed through clinical work with children presenting with treatment resistant epilepsy. Bakke is committed to advancing interdisciplinary competence to ensure the needs of individuals with intellectual disability.

**Katleen Ballon** is a rehabilitation pediatrician working at the Center for Developmental Disorders and the Cerebral Palsy Convention at University Hospitals Leuven, Belgium, focusing on early diagnosis, neurorehabilitation, and multidisciplinary family-centered care. As founder of Villa Clementina, an inclusive childcare center integrating children with and without disabilities, Dr. Ballon promotes equal opportunities and inclusion from early childhood believing in the strength of early intervention, brain plasticity and environmental enrichment. Special interests: Rett syndrome, Smith Magenis Syndrome, Angelman Syndrome, Profound Intellectual and Multiple Disabilities.

**Karen Bindels-de Heus** is a pediatrician specialized in Genetic and Developmental Disorders (EAA) and participating in the multidisciplinary expertise clinics for children with Angelman syndrome (AS), Dup15q, Tuberous Sclerosis Complex, Rett syndrome and cerebral overgrowth disorders of the ENCORE Expertise center at the Erasmus MC Sophia Children's Hospital in Rotterdam, the Netherlands. She defended her PhD dissertation "Angelman syndrome in children" in 2024 and is actively involved in ongoing AS/ Dup15q research. She is member of the ASF Clinical Network, ERN ITHACA and co-founder of the European clinical network for AS & Dup15q.

**Pauline Boiroux** is psychiatrist at Vinatier - CRMR GénoPsy. GénoPsy is a French rare diseases network focused on understanding the genetic and neurobiological aspects of psychiatric disorders. Led by Pr Caroline Demily, it conducts cutting-edge research and provides expert assessments on psychiatric, neurodevelopmental, and behavioral outcomes of rare diseases. The abstract presented here is the work of the GénoPsy team in Lyon, including Dr Albin Blanc, geneticist, Marie-Noëlle Babinet, PhD neuropsychologist and Dr Pauline Boiroux, psychiatrist. Their goal is to improve diagnosis and treatment by exploring the complex role of genetics and brain functions.

**Esther Calame** is a physician assistant (PA) at Basalt, rehabilitation clinic, in The Hague, The Netherlands. She is involved in the care for children and adults with PIMD since 1995, in advance as a physical therapist and since 2019 as a PA. Together with colleagues from various disciplines within and outside Basalt, Esther tries to improve care around the PIMD population and increase knowledge for everyone.
The use of BoNT in the care of this population is still limited and research into the outcomes of the use of BoNT in this group is very desirable.


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**Roseline Caumes,** trained as a paediatrician, she worked for two years in the clinical genetics department at Necker Hospital in Paris, then in neuropaediatrics department in Lille. Roseline currently works as a neuropaediatrician in the clinical genetics department at Lille University Hospital, where she diagnose and monitor patients with genetic neurodevelopmental disorders. She is part of the RADEME research team led by Professor Ghoumid, which is working on MED13L syndrome.

**Helene Cederroth** is Founder and President of the Wilhelm Foundation, an international non-profit dedicated to ending the diagnostic odyssey for People Living With Undiagnosed Diseases (PLWUD). She is a co-founder and permanent board member of the Undiagnosed Diseases Network International (UDNI). She also founded the Undiagnosed Hackathon and Global Undiagnosed Day (April 29). Her work is driven by the loss of three of her four children to an undiagnosed disease, fueling her commitment to ensure no family is left without a diagnosis.

**Agata Cieślikowska is** clinical geneticist and dysmorphologist with over 16 years of experience in pediatric genetics at the Children's Health Centre (IPCZD), currently serving as Head of the Genetic Counseling Clinic. She graduated from the Medical University of Warsaw and completed her specialization in clinical genetics in 2016. Her clinical work focuses on neurodevelopmental and rare genetic disorders, dysmorphology assessment, interpretation of genetic testing, and multidisciplinary care for patients and families.

**Vito Luigi Colona**, MD, graduated in Medicine and Surgery at the University of Rome "Tor Vergata" with an experimental thesis on Parkinson's disease. He worked as a rehabilitation physician and collaborated on biomarker research in neurodegenerative disorders. He specialized in Medical Genetics with a thesis on rare hereditary ataxo-spaslc paraplegias. Currently a Clinical Research Fellow at Bambino Gesù Children's Hospital, he focuses on digital and serum biomarkers in pediatric ataxias and serves as Sub-Investigator in industry-sponsored clinical trials (UNIFAI, PTC Therapeutics).

**Elżbieta Dawidek** is a speech and language therapist, AAC specialist, trainer, and university lecturer affiliated with DSW University of Lower Silesia (Uniwersytet Dolnośląski DSW). Her work focuses on early communication and augmentative and alternative communication, with particular interest in the relationship between language development, cognition, and social interaction in neurodevelopmental conditions. She combines clinical practice, training, and academic research, exploring meaning-making, multimodality, and embodied communication in children with complex communication needs.

**Beatrice Desnous** is MD, PhD child neurologist and clinical neurophysiologist at the University Hospital for Children of La Timone in Marseille, France. She is part of the national reference center for rare epilepsies and the national reference center for rare and severe developmental disorders. She is particularly involved in the care and its coordination of patients with PIMD. Her research deals with the pathophysiology of genetic neurodevelopmental disorders, early detection of neurodevelopmental disabilities, and early intervention.

**Anjuli Dijkmans** is a Dutch medical doctor and PhD candidate at Erasmus MC Center of Expertise for Neurodevelopmental Disorders (ENCORE). Her research focuses on genotype-phenotype in CAMK2-related disorders and identifying feasible outcome measures for future intervention trials.

**Agnies van Eeghen**, MD, PhD, is Intellectual Disability (ID) physician and is specialized in care for children and adults with genetic ID. After her medical specialization, she obtained a PhD on the neuropsychiatric manifestations of Tuberous Sclerosis Complex at Massachusetts General Hospital (Boston, USA). Back in the Netherlands, she set up expert care clinics for adults with Fragile X Syndrome, Tuberous Sclerosis and other rare disorders. In addition to clinical work and chairing the ERN ITHACA guideline working group, Agnies leads a research group, performing trials in TSC, Fragile X syndrome, and Down Syndrome. She develops and implements personalized trial designs and outcome measures, including N-of-1 trials and core outcome sets. Another research line is on the natural history of neuropsychiatric trajectories over all life phases, including dementia. She takes part in various international consortia including the TANDem consortium and GenID Outcome Collaborative.


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**Jos Egger** is professor of Contextual Neuropsychology at Radboud University, Donders Institute, Nijmegen-NL, and scientific director of the Vincent van Gogh Centres of Excellence for Neuropsychiatry, Venray-NL. Being founder of the clinical research group 'Psychopathology and Genetics' in 2007, his research primarily focuses on the cognitive and behavioral aspects of neuropsychiatric and genetic disorders. As program director of the postmaster programs for Clinical psychology/neuropsychology, he strongly advocates the education and professional development of psychological specialists in the field of neurodevelopmental disorders.

**Ellen Elsman:** Ellen Elsman is assistant professor at Amsterdam UMC in the Netherlands, and her research focuses the evaluation and selection of health measurement instruments, with a particular emphasis on patient-reported outcome measures (PROMs). She is affiliated with the COSMIN initiative, and she has conducted multiple systematic reviews of measurement properties of instruments following the COSMIN methodology. She also conducts studies on measurement properties of PROMs for diverse populations, including people with rare genetic neurodevelopment disorders.

**Myriam Essid** is a medical geneticist and aPhD student. My doctoral research focuses on establishing comprehensive clinical and genetic characterizations of rare epileptic syndromes.

**Christian Gebhard** is working as clinical human geneticist in Munich (Germany). Following his training at the Dr. von Hauner Children's Hospital and the Medizinisch Genetisches Zentrum in Munich, he focuses on syndromology, prenatal diagnostics, and tumor predisposition, with a special interest in hereditary endocrine disorders. Christian Gebhard is passionate about using data to improve the patient journey and is committed to empowering patients and their families navigating the challenges of rare diseases.

**Zeineb Ghattassi** is a Child and Adolescent Psychiatrist at Pitié-Salpêtrière Hospital (AP-HP) and Sorbonne University. Her clinical interests focus on neurodevelopmental disorders, supported by five years of experience in a specialized day hospital and her current activity within the Reference Center for Rare Psychiatric Disorders, where she conducts expert NDD consultations. She also has established experience in perinatal psychiatry, including maternity liaison and early childhood (0–3 years) follow-up, and contributes to ADHD parent-training programs and systemic family therapy.

**Maria Giertloval** currently work as a medical geneticist at the Children's Faculty Hospital in Banská Bystrica, as well as at the Department of Clinical Neurosciences, Centre of Clinical and Preclinical Research MEDIPARK, Department of Neurology, Faculty of Medicine, P. J. Šafárik University, Košice, Slovakia. I have 10 years' experience in clinical genetics, with a focus on rare diseases. My main research interests are neurodevelopmental disorders, epilepsy, and neuromuscular disorders, as well as ethnic-specific genetic disorders in the Roma population.

**Anne Gregor** is currently a researcher at the Department of Human Genetics of the Inselspital Bern, Switzerland. She performed her PhD work under the supervision of Christiane Zweier at the Department of Human Genetics in Erlangen, Germany. She did postdoctoral training at the Rockefeller University, New York, USA and again in Erlangen with support from the Deutsche Forschungsgesellschaft and a Marie Slodowska Curie fellowship from the European Commission.

**Tomasz Grybek** is a Patient Advocate, member of the Board of Directors of EURORDIS – Rare Diseases Europe. Member representing patients' organizations nominated by the European Commission to the Paediatric Committee of the European Medicines Agency (EMA PDCO) and Member of the Coordinating Group of the European Network of Paediatric Research at EMA (Enpr-EMA). Patient Advocate involved as an e-PAG Member of ERN-ITHACA and ERN-RND. He is a father of a child living with rare neurological disease called metachromatic leukodystrophy.

**Lusine Harutyunyan** is a PhD researcher at the Center for Medical Genetics (GENERAte – Genetic Epilepsies and Neurodevelopmental Disorders Research Antwerp) at the University of Antwerp. Her research focuses on the genetic Helsmoortel–Van der Aa syndrome, combining systematic clinical phenotyping, neuroimaging, and epigenetic profiling to refine genotype–phenotype correlations. She is particularly interested in expanding the clinical spectrum of rare neurodevelopmental disorders and translating molecular insights into improved diagnostics, patient stratification, and clinically meaningful care pathways across international cohorts.

**Amy van Hattem** is an MD-PhD at the department of Clinical genetics at the Erasmus MC Center of Expertise for Neurodevelopmental Disorders (ENCORE). Her preclinical research focuses on the characterization of novel mouse models for Angelman syndrome and Duplication 15q syndrome. In her clinical work, she aims to further study the role of epilepsy on neurodevelopment in Angelman syndrome, and is finishing up a registry study for the Dutch Duplication 15q patients.

**Alannah Hijlkema** Alannah is a PhD-candidate at the Department of Child and Adolescent Psychiatry & Psychosocial Care and the Department of General Pediatrics at Amsterdam UMC. She holds a Master's degree in Biomedical Sciences, with a specialization in Epidemiology. Her research focuses on validating patient-reported outcome measures (PROMs) and goal attainment scaling (GAS) for individuals with genetic intellectual disabilities. Through her work, she aims to strengthen the integration of the patient perspective in both clinical care and scientific research.

**Maartje ten Hooven – Radstaake,** Dr, she works as an clinical orthopedagogue, lecturer and/or scientist at the Sophia Children's Hospital (Erasmus MC), Radboud University and Stichting Milo. She specializes in individuals with special needs who are non-speaking. She's been a part of the Angelman expertise clinic for 10 years and teaches courses about AAC and dynamic assessment at University. Both areas align, as both focus on rich and robust input and encompassing functional disabilities. With the help of AAC and dynamic assessment, Maartje wishes to enable them to show their communicative and cognitive potential.

**Sylvia Huisman**, MD PhD, is ID Physician and leads expert clinics at Amsterdam UMC and Zodiak, Prinsenstichting. Her current research includes investigating tailored care for individuals with NDD and genetic syndromes exhibiting challenging behavior. She contributes to ITHACA's guidelines on genetic syndromes and on profound intellectual and multiple disabilities (PIMD/polyhandicap). She is a medical advisor for various support groups and scientific advisory committees. Sylvia is dedicated to enhancing interprofessional collaboration and recognizing parents as experts in care.

**Kerstin Kamolane** is a molecular scientist at MVZ genetikum GmbH, Germany, with almost 10 years of experience in diagnostics in human genetics. She's specialized in next generation sequencing (NGS) analysis with focus on neurodevelopmental, cardiac, ophthalmologic and mitochondrial disorders. Kerstin Kamolane holds a Master's degree in Molecular Medicine (M. Sc.) from Ulm University, Germany, which she obtained in 2016. She enjoys learning more about the involvement of non-coding sequence variants in disease.

**Nanda de Knegt** is a neuropsychologist and works as Research Coordinator at a care center for people with intellectual disabilities. She is co-founder of the Dutch Expertise Network about Pain in Intellectual Disabilities. Between 2012-2019, Nanda performed Phd and postdoctoral research on pain assessment in Down, Fragile-X, Prader-Willi, and Williams syndromes. She chaired the committee for the revised Dutch guideline "Pain in adults with intellectual disabilities" (2025) and was co-author of the Ithaca guideline chapter about pain in profound intellectual and multiple disabilities.

**Lindsey Koster** is a Dutch PhD-candidate and physician-researcher. After completing her medical training, she worked as a junior doctor in psychiatry for 1 year. For the past 1.5 years, she has been a physician-researcher on the TEAM DOWN project, studying the course and treatment of depression and DSRD in individuals with Down syndrome, as well as the factors influencing these conditions. Her research also focuses on personalized outcome measures and blood biomarkers for neurodegeneration and Alzheimer's disease in Down syndrome.

**Monika Kowalczyk-Rusak** is clinical geneticist and pediatrician with over 15 years of professional experience, works in Children's Memorial Health Institute in Warsaw. She graduated the Medical University of Warsaw in 2009, subsequently completed pediatric specialization in 2016, clinical genetics specialization in 2025. Her professional experience concerns dysmorphology assessment, interpretation of genetic test results, and managing complex cases of congenital anomalies and rare diseases. She is a member of Polish Society of Human Genetics.



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**Jennifer Kramer** is a research psychologist at the Centre of Excellence for Neuropsychiatry (Vincent van Gogh Institute, Venray, the Netherlands), where she has worked on multiple research projects on (social) cognitive functioning in individuals with Noonan syndrome since 2018. She is also a psychotherapist in Münster, Germany, and is pursuing a PhD at the Donders Institute, Radboud University, Nijmegen, focusing on (social) cognitive functioning and training interventions for individuals with Noonan syndrome.

**Gaetan Lesca**, MD, PhD is a professor of Medical Genetics at Claude Bernard Lyon 1 University. He is leading the reference laboratory for genetic epilepsies at the University hospital of Lyon. In the research field he has contributed to the identification of novel disease-causing genes, phenotype-genotype correlation studies, and functional testing in neurodevelopmental disorders and especially monogenic epilepsies. He is chair of the working group on genetic research of ERN-EpiCARE and member of the Commission on Genetics of the International League Against Epilepsy (ILAE).

**Liselot van der Laan** is a scientist specializing in genomic and epigenomic mechanisms underlying neurodevelopmental disorders. Her work focuses on integrating DNA methylation profiling, long-read sequencing, and functional assays to improve molecular diagnostics for rare conditions. She has contributed to the identification and characterization of episignatures associated with sequence variants, CNVs, and environmental disorders. By combining genome-wide analyses with patient-derived cellular models, she aims to advance precision diagnostics and deepen our understanding of disease biology.

**Ben Jemaa Lamia** is Professor of medical genetics in Faculty of Medicine of Tunis and the head of department of genetics in mongi slim hospital la Marsa Tunis Tunisia. She is vice President of the Tunisian Society of Medical Genetics and director of the “mother-child” research laboratory at Mongi Slim Hospital. Her research centers are congenital malformations, chromosomal abnormalities , genetics of intellectual disabilities and genetics of epilepsy.

**Marit van der Leij** is a medical student with a bachelor’s degree in biomedical sciences and a research background in rare neurodevelopmental disorders. Her work focuses on identifying prevalences and core clinical characteristics of these conditions. Marit is particularly interested in bridging research and clinical practice to improve understanding and care for individuals with rare neurological disorders.

**Ewelina Knapska**, PhD, is a Professor at the Nencki Institute of Experimental Biology in Warsaw, where she leads the Laboratory of Neurobiology of Emotions. Her research explores neural circuits underlying social behavior, emotional contagion, and sensory processing. By integrating animal models with human studies, her work provides mechanistic insights into how social signals shape brain function, with relevance to neurodevelopmental disorders, including tuberous sclerosis complex.

**Katarzyna Kotulska** is the professor and head of the Department of Neurology and Epileptology at The Children’s Memorial Health Institute, Warsaw, Poland (member of ERN EPICARE). Dr Kotulska is certified in neurology and neuropediatrics. She is a representative of Poland in the European Union Board of Member States for European Reference Networks and a member of Polish National Council for Rare Diseases. Dr Kotulska is also a member of the Neurobiology and the Neurological Sciences Committees of the Polish Academy of Sciences. Dr Kotulska’s clinical and basic research focuses mainly on rare diseases of the developing nervous system and epileptology. She is particularly interested in rare diseases associated with epilepsy, like tuberous sclerosis complex, and rare neuromuscular diseases in children, especially spinal muscular atrophy. Dr Kotulska coordinates the national program of Spinal Muscular Atrophy treatment in Poland.



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**Joana Matos** is Child Psychiatrist, Full-time Hospital Practitioner in Prof. David Cohen's department at the Pitié-Salpêtrière Hospital, Paris, France, since 2008. Physician in charge of the Language and Learning Disorders Referral Center in the department, which treats young people with very complex developmental disorders. In terms of research, he participates in ongoing research projects in the department, particularly on the genetic etiology of developmental disorders and the benefits of using a serious game based on musical rhythm for oral and written language disorders and attention disorders. Coordinates projects using movement and dance as therapeutic tools for sensory integration, coordination, and executive function disorders. Member of the scientific committee for the Master's in Music and Therapy (a collaboration between the Faculty of Medicine and the Faculty of Arts at Sorbonne University).

**Magdalena Mroczek** is a board-certified neurologist and clinical scientist with an interest in neurogenetics, neuromuscular disorders, and rare diseases. Magdalena is recently interested in central nervous system involvement in neuromuscular diseases and neuropsychiatric symptoms. She completed several fellowships in these areas (Neurogenetics Lab, UCL Prof Houlden; JWMDRC, Newcastle University). She currently works as an attending physician at the Clinic for Consultation-Liaison Psychiatry and Psychosomatics, University Hospital Zurich, and as a visiting fellow at the Human Genetic Imaging Group, University of Basel.

**Hatice Mutlu** is an Associate Professor of Pediatric Genetics at Ankara University, specializing in rare disease genomics and advanced sequencing technologies. Her research focuses on long-read genome analysis, structural variant detection, and genotype–phenotype integration in undiagnosed pediatric disorders. She leads multiple national and international projects employing whole-genome sequencing, radiogenomics, and functional modeling to improve diagnostic yield in rare diseases. Dr. Mutlu also contributes to the development of innovative genomic panels and precision medicine tools.

**Heidi Elisabeth Nag** has worked at Norwegian Centre for Rare Diseases, unit Frambu as a special educational advisor since 2005. Frambu is one of nine units for rare disorders in Norway Heidi mainly works with and does research regarding rare disorders with neurodevelopmental disabilities and is especially interested in challenging behaviour and communication. In 2020 she finished her PhD in Educational Science with the topic: Behavioural Phenotypes of Smith-Magenis syndrome (SMS).

**Mana Nasori** is a PhD-candidate at the department of Child and Adolescent Psychiatry & Psychosocial Care at the Amsterdam UMC. With a Master's in Management Policy and Entrepreneurship in Health and Life Sciences, her research focusses on interprofessional collaboration around challenging behaviour of people with rare genetic intellectual disability syndromes (RGIDS). She investigates how healthcare professionals from hospitals, mental healthcare and intellectual disability care can collaborate interprofessionaly, with a specific focus on how parents' experiential knowledge can contribute to this collaboration.

**Cindy Navis** has been working at the Sophia Children's Hospital - Erasmus MC since 2011, where she has specialized in feeding problems and augmentative and alternative communication (AAC) for children with multiple disabilities. As an experienced professional, she is part of the ENCORE expertise teams, collaborating closely with multidisciplinary teams to optimize care for children with complex conditions. Her dedication to improving the quality of life for children with complex care needs is at the heart of her professional commitment.

**Sylvie Odent** is a professor of medical genetics (Rennes University Hospital, Clinical Genetics Department, University of Rennes). She is affiliated with the Institute of Genetics and Development in Rennes (IGDR), where she focuses on the genetics of brain malformations. She coordinates the Rare Diseases Reference Center "Developmental Anomalies and Malformation Syndromes" in Western France (CLAD-Ouest), which is part of the AnDDI-Rares network and the European ERN ITHACA network. She is vice-president for "care" of the 4th French Rare Diseases Plan.

**Carmen Oldenboom** is a PhD student at the Centre of Excellence for Neuropsychiatry, Vincent van Gogh Institute for Psychiatry in Venray, the Netherlands. Her PhD focuses on neuropsychological functioning in rare genetic disorders, including PTEN-Hamartoma Tumor syndrome, Koolen-de Vries syndrome, and CAMK2-related conditions. She works as a psychologist and is currently enrolled in the Healthcare Psychologist programme (post-master) at STEVIG, a healthcare organization for people with mild intellectual disabilities in Oostrum.


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**Katrin Õunap** graduated as a pediatrician at the University of Tartu and later specialized in medical genetics. She is defended her PhD thesis in 1999. Presently, Katrin Õunap is working as a professor of clinical genetics at the University of Tartu. Her research team's primary research focus is discovering new rare disorders. She leads the Competence Centre of Rare Diseases at Tartu University Hospital and serves as the Chief Specialist for Rare Diseases at the Ministry of Social Affairs in Estonia.

**Radhakrishnan Periyasamy:** Dr. Radhakrishnan Periyasamy is a postdoc in medical genetics at University Hospital Basel, Switzerland. He earned a Ph.D. in medical genetics, where he investigated the genetic causes of lethal fetal malformations. He formerly worked as an assistant professor in India, where he specialized in NGS data analysis and variant interpretation in rare disorders. His current research, which is supported by an SNSF grant, combines WGS and fetal tissue RNA-seq analysis to reveal processes driving prenatal developmental abnormalities. His interests include rare disease genomics and multi-omics integration.

**Ana Roche:** Dr Ana Roche MD PhD is a Pediatric Neurologist working now in Sabadell, Barcelona, where she combines clinical consultation with research at Parc Taulí University Hospital and I3PT (Parc Taulí's Institute for Research and Innovation) and the Universitat Autònoma de Barcelona (UAB), with especial interest in neurodevelopmental disorders and rare diseases.
She is the clinical coordinator of the Fragile X and Angelman Clinics at Parc Taulí, participating in various phase I-II and III clinical trials with advanced therapies.

**Andreas Roos:** As senior scientist I am working in the field of translational medicine with a main focus on rare neurodegenerative and neuromuscular disorders. In order to understand the etiology of these diseases and to obtain a full picture, my work focusses on the identification of the genetic cause as well as on the discovery of the related pathophysiological consequences. For the latter purpose, various biochemical techniques including different proteomic approaches are applied by making use of in vitro and in vivo models as well as of patient-derived material.

**Marie-Christine Rousseau:** Dr. Marie-Christine Rousseau, MD, PhD, is a specialist in Physical and Rehabilitation Medicine at the University Hospital of Paris (AP-HP), France. She leads research on PIMD/Polyhandicap within the French Polyhandicap Federation of the University Hospitals of Paris (AP-HP). Her work focuses on coordinating research projects aimed at improving knowledge and care for individuals with PIMD/Polyhandicap. She is also a member of the national reference center for PIMD/Polyhandicap.

**Anja Bos-Roubos** is a clinical neuropsychologist and Ph.D. candidate at the Center of Excellence for Neuropsychiatry at the Vincent van Gogh Institute for Psychiatry in Venray, the Netherlands. She focuses on diagnosing and treating the cognitive and behavioral aspects of neuropsychiatric and genetic disorders, such as Prader-Willi syndrome, neurofibromatosis type 1, and 16p11.2 deletion syndrome. She is a member of several multidisciplinary specialist teams at the Erasmus Medical Center in Rotterdam and the Maastricht University Medical Center. Additionally, as a scientist-practitioner in clinical neuropsychology, she contributes to patient advocacy initiatives in the Netherlands and internationally. Currently, she participates in the international SATB2 Guideline Working Group.

**Paulina Rutka:** Paulina Rutka is a psychologist, speech and language therapist, and AAC specialist supporting individuals with complex communication needs. She has worked across early intervention, psychological–pedagogical counseling, and diverse educational settings, providing consultations, training, and supervision for families and professionals. She is the co-founder and president of the generAACja Foundation, which promotes evidence-based AAC interventions and communication accessibility in Poland.

**Catherine Saint-Georges:** Catherine Saint-Georges works as a child psychiatrist in a parent-infant consultation unit in Paris. She's also responsible of a care unit dedicated to children with Autism Spectrum Disorders in Salpêtrière Hospital. Her field of research, interests and publications deals with early signs of autism, including emotion, sychrony and reciprocity in early interactions, preemtive interventions and also evaluations of intervention for chidren with ASD and DI.


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**Alfi Aran Shukur:** I, Alfi Aran Shukur, am a sixth-year medical student at Ankara University with a strong focus on neurodevelopmental and neurogenetic disorders. I conducted research in neuroimaging, radiogenomics at Interventional MR Clinical R&D Institute and Department of Pediatric Genetics, Ankara University. Moreover, I also worked on MRI-based analysis of multiple sclerosis at the University of Basel's ThINk Group. I presented my radiogenomics project at European Society of Human Genetics Congress 2025 in Milan and received a national competitive funding from TÜBİTAK—the Scientific and Technological Research Council of Türkiye. I currently study imaging and computational methods to better understand neurogenetic disorders.

**Karolina Śledzińska:** Karolina Śledzińska, MD, PhD, is a pediatrician and clinical geneticist with a special interest in rare diseases. She works at the Department of Pediatrics, Hematology and Oncology at the Medical University of Gdansk and at the Genetics Outpatient Clinic of the University Clinical Centre, Gdańsk, Poland. She is an academic teacher and researcher, involved in the Rare Diseases Centre and representing the Gdansk center in ERN ITHACA and ERDERA.

**Leendert Sneep** is physiotherapist, lecturer and pain consultant at Ipse de Bruggen – a care institution for people with intellectual disability. He co-authored the Dutch guideline on pain in people with intellectual disabilities (Pijn bij mensen met een verstandelijke beperking, SKILZ, 2025) and the part about pain of the Ithaka guideline on Profound Intellectual Multiple Disabilities (Guidelines & consensus (WG11) - ERN ITHACA). Leendert is co-initiator of Pain Care Unlimited - Dutch knowledge network on pain in intellectual disabilities (PijnZorg (On)beperkt).

**Ilaria Svezia** holds an MSc in Cell and Molecular Biology from the University of Rome "Tor Vergata" (UTV), where she completed an experimental thesis on a rare RNF220-associated autosomal recessive leukodystrophy (AR-LAD). She is currently a Research Fellow at Bambino Gesù Children's Hospital in Rome and a PhD candidate in Biochemistry and Molecular Biology at UTV. Her research focuses on the molecular mechanisms of RNF220-associated AR-LAD and on rare tubulinopathies, combining patient-derived iPSC models with neurobiological approaches.

**Carme Torrents** is a pediatric neurologist with expertise in neurodevelopmental disorders. She currently works at Parc Taulí Hospital in Sabadell (Barcelona, Spain), with a special focus on a Child Development and Early Care Center. Her work centers on the early detection and intervention of neurodevelopmental conditions. She has completed the International Training Program in Neurodevelopmental Disorders at the MIND Institute (California, US) and has experience in both clinical practice and research in early childhood development and rare genetic diseases.

**David Townend** is Professor of Health and Life Sciences Law at The City Law School (CLS) in City St George's, University of London. He is an academic lawyer specialising in data governance. He examines the governance of modern data science: theoretical issues of law and ethics, and concepts of property and privacy; and substantive issues of personal information and data protection and commercial interests in data and information. Professor Townend is Associate Dean for Research at CLS.

**Gillian Townend** is a Lecturer (Speech and Language Therapy) at the University of Reading and Research Lead for Rett UK. She was formerly a researcher at the Rett Expertise Centre Netherlands and led the international project to develop the Rett Syndrome Communication Guidelines (published in 2020). She continues to work with Rett Associations globally to translate the Guidelines into multiple languages and to explore their impact and implementation within everyday environments and in clinical practice.

**Ellen Wingbermühle** is a clinical neuropsychologist and senior researcher at the Centre of Excellence for Neuropsychiatry, Vincent van Gogh Institute for Psychiatry, Venray (NL). Her work focuses on research, diagnostics, and clinical management of Rasopathies and other rare genetic disorders. She is a member of several multidisciplinary specialist teams at the Radboudumc Expert Centre for Rare Developmental Disorders. In addition, she serves as head of residency in clinical neuropsychology at Vincent van Gogh, lectures and supervises in postgraduate training programmes, and PhD projects.



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**Anzhela Yervandyan**, MD, is a medical geneticist in the Center of Medical Genetics and Primary Healthcare in Yerevan and a member of the “Armenian Society of Human Genetics” and “National Center of Expertise for Rare Diseases

**Nikolinka Yordanova**, MD, PhD obtained her specialty in Paediatric Endocrinology in 2020. In 2024, she successfully defended her PhD thesis in the field of rare endocrine diseases under the supervision of Prof. Violeta Iotova. Since 2018, Dr. Yordanova has been the head of a multidisciplinary team providing care for patients with Prader–Willi and Silver–Russell syndromes at the Varna Expert Centre for Rare Endocrine Diseases (UMHAT “Sveta Marina, Varna, Bulgaria), which is part of the Endo-ERN.

**Ilse Zaal-Schuller** is an ID-physician, palliative care specialist, and researcher, with special expertise in the care of people with PIMD and in medical ethics. She works at Prinsenstichting, a care organization for people with ID, and at Amsterdam UMC, where she is affiliated with an academic outpatient clinic for people with PIMD. As a researcher, she is involved in several studies on (pediatric) palliative care for people with ID. She has several national peer-reviewed publications and contributes to national guideline development.

# Meet our scientific committee

**Krystyna Chrzanowska**, MD, PhD, is specialist in pediatrics and clinical genetics, full professor at the Children's Memorial Health Institute (CMHI) in Warsaw and head of the Department of Medical Genetics (2017-2023). Areas of scientific interest: clinical and molecular aspects of chromosomal/genomic instability syndromes, dysmorphic syndromes, intellectual disability, imprinting disorders and childhood malignancies. Co-author of 250 original publications. National coordinator of the Orphanet Poland (2017-2025) and leader of ONW and OD4RD projects. Representative of the CMHI in the Board of ERN-ITHACA Network. Member of Polish Council of Rare Diseases, one of the authors and chief of the National Plan for Rare Diseases.

**Dorica Dan** initiated RPWA (Romanian Prader Willi Association) in 2003, established RONARD (Romanian National Alliance for Rare Diseases) in 2007 and Romanian Rare Cancers Association in 2011. She initiated the National Plan for Rare Diseases in Romania. In June 2011 she has opened the Pilot Reference Center for Rare Diseases "NoRo". She is the mother of a daughter with Prader Willi Syndrome. Dorica Dan is ePAG chair in ITHACA and was appointed vice-president of Eurordis in 2022 and has been a member of the EURORDIS Board of Directors since 2007.

**Laura de Graaff** is associate professor Internal Medicine for Rare Genetic Syndromes (RGS) and founder of the Erasmus MC Center for adults with RGS in Rotterdam, the Netherlands. In 2015 she finished her medical training in Internal Medicine-Endocrinology and launched the Center for adults with RGS. Its multidisciplinary team takes care of over 1100 adults with over 90 (ultra-) rare genetic syndromes. Dr. de Graaff leads both clinical research and fundamental research lines investigating biomolecular pathways and cellular mechanisms involved in rare endocrine genetic syndromes.

**Sylvia Huisman**, is an Intellectual Disability Physician, demonstrated in her PhD research a translational and transdisciplinary approach is the basis for understanding and treatment of self-injurious behavior. Current research areas: 'Modelling NDD and mosaicism in CdLS using human brain organoids', 'Tailor made care for people with NDD and genetic syndromes with challenging behavior: interprofessional collaboration and parents as experts' and 'Tacit Knowledge: implicit expertise in the care for people with PIMD'. Sylvia runs expert clinics at Amsterdam UMC and Zodiak. She is active in ITHACA's guidelines for genetic syndromes and PIMD

**Claudine Laurent-Levinson** is a child psychiatrist at Hôpital Pitié-Salpêtrière and a faculty member (MCU-PH) at Sorbonne University (Paris, France). She completed her PhD (Neurosciences), trained in clinical genetics and received post-doctoral training on proteomics (Vanderbilt University and NIMH). She was Associate Professor of Child Psychiatry at Stanford University (2013-2016). She leads a clinical research group (clinical and genetic characterization of early-onset psychoses), and is interested in specific learning disabilities. She belongs to the PGC schizophrenia group. She has published more than 100 peer-reviewed articles.

**Gaetan Lesca**, MD, PhD is a professor of Medical Genetics at the University Claude Bernard Lyon 1. He is leading the reference laboratory for genetic epilepsies at the University hospital of Lyon. In the research field he has contributed to the identification of novel disease-causing genes, phenotype-genotype correlation studies, and functional testing in neurodevelopmental disorders and especially monogenic epilepsies. He is co-chair of the working group of genetic research of the ERN-EpiCARE and co-chair of the task force on Genetic Testing of the International League Against Epilepsy (ILAE).



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**Tjitske Kleefstra** is a clinical geneticist dedicated to study underlying mechanisms and clinical consequences of genetic neurodevelopmental disorders. She is Head of the Department and professor in Clinical Genetics at ErasmusMC Rotterdam, where she is affiliated to the expert center ENCORE and the Sophia Children Hospital. In addition, she is appointed endowed professor at the Radboudumc Nijmegen (with support of the Vincent van Gogh center for Neuropsychiatry, Venray) where she has founded the Radboudumc expert center for rare genetic neurodevelopmental disorders. As clinician-scientist and executive board member and chair of the working group on NDD in ITHACA, she closely participates both with professionals and with Patient Advocacy Groups and therefore is excellently positioned to implement fundamental research findings and studies tightly linked to the patients in a regional and global network.

**Agnieszka Madej-Pilarczyk**, MD, PhD, is specialist in clinical genetics and internal medicine and Head of the Department of Medical Genetics, Children's Memorial Health Institute (CMHI) in Warsaw. Areas of scientific interests: laminopathies, genetic aspects of rare diseases, including dysmorphic syndromes, intellectual disability, muscular dystrophies, myopathies, collagenopathies and rare cardiac diseases. Co-author of 70 papers. Country coordinator of Orphanet Poland since 1st January 2026. Substitute representative of the CMHI in the Board of ERN-ITHACA Network. Member of Polish Council of Rare Diseases.

**Stephanie Miot** is a geriatrician and psychiatrist by training. She has a geriatric consultation for aging adults with neurodevelopmental disorders (NDD) in University Hospital of Montpellier. She is also developing a dedicated health care network for these adults in Occitanie, France. Neurobiologist trained at *the Liliane Bettencourt INSERM-School* (French MD-PhD program) and alumnae of the For Women in Science – L'Oréal Unesco program, she studies aging trajectories of NDD adults within the Centre de recherche en Epidémiologie et Santé des Populations (CESP, INSERM U1018) and is interested in identifying biomarkers of pathological aging in this population.

**Marie-Christine Rousseau** is specialized in physical and rehabilitation medicine and in charge of clinical research for the French Polyhandicap Hospital Federation, Assistance Publique Hôpitaux Paris.

**Katarzyna Świeczkowska**, vice-president of PSONI Gdańsk, is a parent of a person with PWS, educator, co-founder and a director of the Group of Non-Public Educational Institutions in Polish Association for Persons with Intellectual Disability in Gdańsk. Katarzyna Świeczkowska is a member of EPAG at the ERN ITACHA and the Patient Council at the Center for Rare Diseases in Gdańsk. Since 2020, she has been cooperating with EACD, IAACD, Canadian association CanChild and the Polish Academy of Childhood Disability. For several years, she has been a board member of the international organization CARAVAN 2000, European Movement for Diversity and Understanding and the Polish AAC and ETR Council.

**Marco Tartaglia** is senior scientist and head of the *Molecular Genetics and Functional Genomics* Research Unit at the *Ospedale Pediatrico Bambino Gesù*, Rome, Italy. Previously (2005-2015), he served as Director of the *Molecular and Cellular Endocrinology* and *Physiopathology of Genetic Diseases* Research Units at the *Istituto Superiore di Sanità*, the *Italian National Institute of Health*. His research is focused on the understanding the molecular bases of disorders affecting development and growth. His work has contributed to the discovery of more than 50 novel disease genes and clinically profile a high number of previously uncharacterized disorders. A major longstanding research interest is focused on RASopathies, with efforts that have mainly been directed to identify the genes implicated in these disorders, elucidate the molecular mechanisms underlying pathogenesis, and delineate clinically relevant genotype-phenotype correlations. Among the major research outputs, there is the identification of *PTPN11*, *KRAS*, *SOS1*, *RAF1*, *SHOC2*, *CBL*, *NRAS*, *SOS2*, *RRAS2*, *MAPK1*, and *SPRED2* as genes implicated in these diseases. He also discovered the oncogenic role of a class of *PTPN11* mutations in juvenile myelomonocytic leukemia and other childhood leukemias, providing the first evidence of a protein phosphatase acting as an oncoprotein when mutated. His work has contributed to recognize the RASopathies as a new cancer-prone family of diseases caused by upregulated RAS signaling and characterize novel mechanisms and circuits by which intracellular signaling dysregulation through RAS proteins and their effectors perturbs development but not necessarily contributes to oncogenesis.



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**Şehime Gülsün Temel,** Prof., MD, PhD, graduated from Bursa Uludağ University Faculty of Medicine and earned her PhD in Histology and Embryology. She later completed a second PhD in Medical Genetics and holds full professorship in both disciplines. She conducted NIH-funded postdoctoral research at the University of Kentucky, focusing on the female reproductive system, neuroendocrine mechanisms, and aging. She is the founding chair of Translational Medicine and currently serves as Head of the Department of Medical Genetics at Bursa Uludağ University. She is also CEO of MyGene at ULUTEK Technopark, leading translational research and innovation initiatives.

**Zeynep Tümer** is a medical doctor by training and after completing PhD studies on the X-linked copper metabolism disorder Menkes disease in 1996, ZT's research interest has been focused on understanding the underlying genetic mechanisms of rare NDDs. Currently, ZT is employed at the Copenhagen University Hospital, Rigshospital and affiliated to the University of Copenhagen as professor. Apart from research she is carrying out genetic diagnosis of patients with intellectual disabilities and imprinting disorders. She has 220 peer-reviewed publications and has supervised 25 PhD students, 12 PostDocs, and more than 80 Master/bachelor students.

**Alain Verloes**, MD, PhD, is a clinical geneticist, professor of Medical Genetics in Paris Cité University Medical School, and head of the department of Medical Genetics in Robert DEBRE University Hospital, in Paris, France. He is coordinator of a French Rare Diseases Reference Centre dedicated to Developmental Anomalies since 2005. Since 2019, he coordinates ERN ITHACA, the European RD Reference Network dedicated to Dysmorphology (abnormal development) and NeuroDevelopmental Disorders, including intellectual disabilities and autism spectrum disorders. His research interests focus on RASopathies, primary microcephalies and the monogenic forms of intellectual disabilities.

**Ayça Yiğit** is a PhD candidate in Molecular Biology and Genetics at İzmir Biomedicine and Genome Center (IBG). Her research focuses on molecular genetics and rare disease genomics, including whole genome sequencing and integrative multi-omics approaches for improving genetic diagnosis. She is actively involved in clinical genomic analyses and translational research projects, particularly within the RareBoost initiative. Her research interests include the genetic basis of neurodevelopmental disorders, with a particular focus on the genetics of Cerebral Palsy."

**Christiane Zweier** is head of the Department of Human Genetics at the University Hospital in Bern, Switzerland. She is a clinical geneticist by training and from the beginning also has had a large interest in research. She is coordinating and contributing to the SysNDD database, and her research group focuses on the identification and characterization of known and novel NDDs and other rare diseases by using high throughput sequencing technologies and model systems such as IPSCs, organoids and *Drosophila melanogaster.*



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