Abstract book

Poster presentation

EuroNDD 2024

Second European Workshop for a multidisciplinary view on rare genetic neurodevelopmental disorders

April 4, 2024, Lisbon

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ID 11

GenIDA, an international participatory database to better characterise comorbidities of genetic forms of intellectual disability: Novel findings on KBG, SETD5 and DDX3X syndromes

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GenIDA is an international participatory registry (https://genida.unistra.fr/) aimed at better characterizing the clinical manifestations and natural history of genetic forms of intellectual disability (ID) with or without autism spectrum disorder (ASD) or epilepsy. Clinical information reported by the patient's family using a structured questionnaire is analysed to identify new medically relevant information for families and professionals concerned with a given condition. The questionnaire consists of 41 multiple-choice questions exploring physical parameters, cognitive and behavioural aspects, the presence or absence of neurological disorders or problems affecting the main physiological functions, etc. Five open-ended questions explore families' perceptions of the events that most affect their relative's health and quality of life, treatment secondary effects, etc. [1]. The questionnaire is currently available in 8 languages and has been completed for over 1880 patients, the main cohorts being Koolen-de Vries (n=274) and Kleefstra (n=215) syndromes [2], while other cohorts have grown significantly over the past year.

KBG syndrome, characterized by ID and some recognizable dysmorphic traits, is due to deleterious *ANKRD11* variants. Variants in *SETD5* were identified some 10 years ago as responsible for a KBG-like phenotype. As the 2 conditions can hardly be distinguished clinically, we used GenIDA to evaluate the benefit of patient empowerment on clinical characterization of these syndromes. This approach enabled us to highlight quality of life issues, such as the consequences of epilepsy and ID for KBG individuals (n=57), or gastrointestinal and eating problems for SETD5 individuals (n=37).

Pathogenic *DDX3X* variants are emerging as one of the most common genetic causes of ID in females, accounting for 1-3% of cases, and have been associated with a specific phenotype, including hypotonia, and ASD. Data collected for DDX3X individuals in GenIDA (n=62) were analysed to extend this phenotypic description: our results are consistent with the literature regarding the importance of ADHD, sleep disorders, and delays in developmental milestones in these individuals, who generally turn out to be minimally verbal (childhood apraxia of speech being a common feature). Behavioural problems, meanwhile, appear to be far more significant for caregivers than reported in the literature: in addition to ADHD, over 30% of caregivers report severe daily problems with impulsivity, stereotypies and anxiety.

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These results validate the interest of our participatory approach: through their direct involvement, families can reveal previously underestimated aspects of the disorder and highlight their major concerns in their daily lives. More than a complement to medical reports, GenIDA can be used by specialists for "prospective phenotyping" to consolidate knowledge of ID syndromes and improve prognosis and patient management.

References

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ID 39

CSMD3 as a potential candidate for neurodevelopmental disorders

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Background: CUB and Sushi multiple domains 3 (CSMD3) is a large transmembrane protein that is highly expressed in adult and fetal brain tissue. *CSMD* family genes have been associated with epilepsy, schizophrenia and autism spectrum disorder (ASD) in literature, however they are not connected to any syndromes in the Online Mendelian Inheritance in Man® database. *CSMD3* function is an active topic in research, studies have indicated its involvement in dendritic branching and morphology, including the development of cerebellar Purkinje cells (PC). Recently, Xi et al (2023) described *CSMD3* knockout mice that exhibited abnormal PC morphology, intrinsic excitability, and impaired synaptic plasticity. Additionally, the mice presented with core autistic-like symptoms and motor dysfunction, implicating CSMD3 impairment as a potential cause of ASD.

Methods: Using Matchmaker Exchange platform, we have collected clinical data about seven patients with rare compound heterozygous (cHet) and four patients with *de novo* heterozygous (Het) variants in *CSMD3* gene.

Results: The variants are located in different domains and regions across the CSMD3 protein (Fig 1). Patients are predominantly male (male to female ratio 5:2 among cHet and 3:1 among Het). The median age during last evaluation is higher in the cHet group (11 years, range 5-23) compared to Het group (3 years, range 1.25-4.6 years). Most patients are of European descent with two exceptions in both groups. All patients with cHet variants have developmental delay, however the clinical severity and type varies. Intellectual disability (ID) is present in 4/7. Most patients in the Het group have normal development (3/4) and they were all too young for evaluating ID during last visit. Hypotonia is relatively

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common in both cHet and Het group, 3/7 and 2/4, respectively. Autistic features were described in 3/7 patients in the cHet group. Brain MRI has been done in five patients with cHet variants and two patients with Het variants, structural abnormalities were seen in 3/5 and 1/2, accordingly.

Conclusion: In conclusion, we did not see a clearly definable syndrome among patients with variants in *CSMD3*. However, we still believe that it is a good candidate for their neurodevelopmental phenotypes and the varying clinical expressivity might be attributed to the different locations of the variants. Further research in a larger cohort and with functional studies is necessary to confirm this hypothesis.

Grants: PRG471

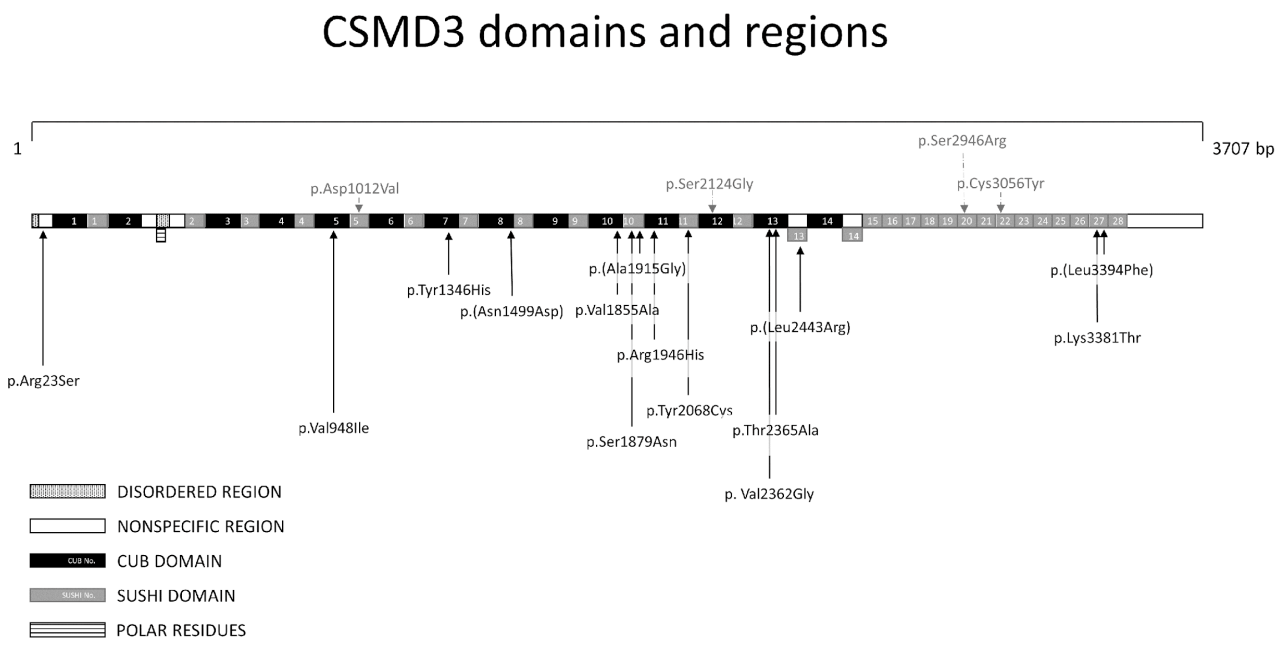

Figure 1. Schematic representation of the CSMD3 variants found in our cohort. Heterozygous variants are in light grey above and compound heterozygous variants are in black below the protein. CUB domains are represented by black rectangles and SUSHI domains by gray. The domains and regions are based on information available in UniProt database. bp – base pairs

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New insights in 9q21.13 microdeletion syndrome: Genotype–phenotype correlation of 28 patients

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The implementation of array comparative genomic hybridisation (array-CGH) allows us to describe new microdeletion/microduplication syndromes which were previously not identified. 9q21.13 microdeletion syndrome is a genetic condition due to the loss of a critical genomic region of approximately 750kb and includes several genes, such as *RORB* and *TRPM6*.

Here, we report a case of a 7-year-old boy affected by 9q21.13 microdeletion syndrome. The psychomotor developmental milestones were reached late: he started walking at 18 months and speaking at 4 years. Because of psychomotor delay associated with poor participation/language, the tendency to isolate and elusive eye contact, our patient began neuropsychiatric investigations and, when he was 18 months old, he started psychomotricity and speech therapy with good clinical improvements. When he was 2 years old, he presented absence seizures controlled by treatment with valproic acid. The electroencephalogram revealed bilateral middle parieto-temporal paroxysmal anomalies and rapid onset activity in the right temporal region. At the age of 2 years and 2 months, he underwent ophthalmological consultations with evidence of severe myopia which was treated with corrective lenses. When he was 4 years old, he did a brain MRI which showed symmetrical hyperintensity of the peri-trigonal white matter (**Figure 1A**) and prominent mesial subarachnoid peri-temporo-polar space (**Figure 1B,C**). At our genetic evaluation, he presents upslanted palpebral fissure, hypertelorism, high palate, long philtrum, wide mouth, thin upper lip vermilion (**Figure 2A,B**), clinodactyly of the 5th finger, short hands (**Figure 2C,D**), and sandal gap (**Figure 2E**). For these reasons, the patient underwent genetic investigations: array-CGH was performed *in trio* and showed a *de novo* deletion on chromosome 9, in the region 9q21.13q21.31 (75,505,408-83,868,435 bp; assembly: grch37/hg19), extending for approximately 8,363 Mb. In summary he has global developmental delay, intellectual disability, autistic behaviour, seizures and facial dysmorphism. Moreover, he has severe myopia, which was previously reported in only another patient with 9q21.13 deletion, and brain anomalies which were never described before in 9q21.13 microdeletion syndrome.

We have done a literature overview of the 17 patients described before with 9q21.13 microdeletion syndrome and we have collected all the 42 DECIPHER patients with a deletion in 9q21.3 locus overlapping with the deletion of our patient. We excluded the DECIPHER patients without clinical information available and the duplicate patients who were described in the literature and also present in DECIPHER database (**Figure 3**). In order to better investigate the four candidate genes *RORB, TRPM6, PCSK5*, and *PRUNE2* for neurological phenotype, we make, for the first time, a classification in four groups of all the collected 28 patients (including our case).

To better study 9q21.13 microdeletion syndrome and each specific region, we have decided to stratify all the patients into four groups. This classification is based both on the genomic position of the deletions included in the 9q21.3 locus deleted in our patient and on the different involvement of the four-candidate gene (**Figure 4**). In this way, we compare the clinical problems, the radiological findings, and the dysmorphic features of each group and of all the collected 28 patients (**Table 1**).

The genotype–phenotype comparison of all the reported 28 patients reveals several common key features (such as intellectual disability, autistic behaviour, seizures, abnormal eye physiology, and brain anomalies), but also a great phenotypic heterogeneity.

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Abnormal eye physiology is frequent in all the groups except for Group 2B, and it is mostly present in Group 1 (38.5%) and Group 3 (33.3%), confirming the importance of the involvement of *RORB* and *TRPM6* for the ocular phenotype. Particularly, our patient presents severe myopia, reported in only one patient (DECIPHER case 254951). These frequencies show us how ocular problems are relevant in 9q21.13 microdeletion syndrome.

Furthermore, the brain MRI alterations are present in 40% of patients from Group 2A and in 23.1% of patients from Group 1. Chiari type I malformation, hippocampal asymmetry, hypoplasia of corpus callosum, delayed myelinisation, and arachnoid cyst are reported. Our patient's MRI findings have never been described before in 9q21.13 microdeletion syndrome and they include symmetrical hyperintensity of the peri-trigonal white matter and prominent mesial subarachnoid peri-temporo-polar space.

Regarding dysmorphic features, patients from Group 3 present higher frequencies among the other groups: low anterior hairline and hypertelorism are the most common features (both 100%), followed by long philtrum (50%), high palate (50%), thin upper lip vermilion (50%), and upslanted palpebral fissure (50%). We think *RORB* and *TRPM6* could be responsible for the dysmorphic features of 9q21.13 microdeletion syndrome.

In summary, we describe a rare syndrome in which the main clinical features could be most likely caused by the loss of *RORB* and *TRPM6*, which is deleted in patients affected by 9q21.13 microdeletion syndrome and we propose a *baseline ophthalmological* and *neurological monitoring* of this syndrome. The description of further patients with the deletion in 9q21.13 locus and the clinical updating of the already described 28 patients is desirable to ensure an adequate and targeted follow-up of this very peculiar and rare syndrome, to monitor its continuous clinical evolution and to evaluate a proper follow-up.

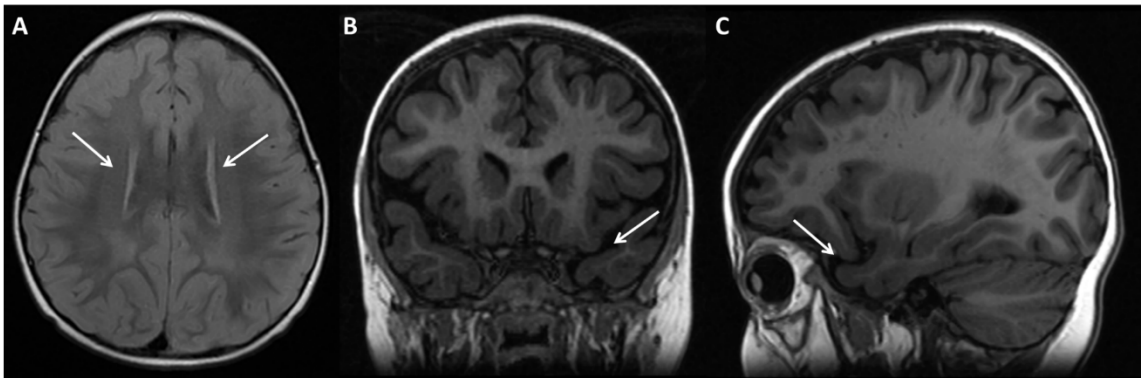

Figure 1. Brain MRI in T2 FLAIR of our patient. (A). Symmetrical hyperintensity of the peri-trigonal white matter (as indicated by the white arrows. (B-C). Prominent mesial sub-arachnoid peri-temporo-polar space (as indicated by the white arrows). In axial (A), coronal (B) and sagittal (C) images.

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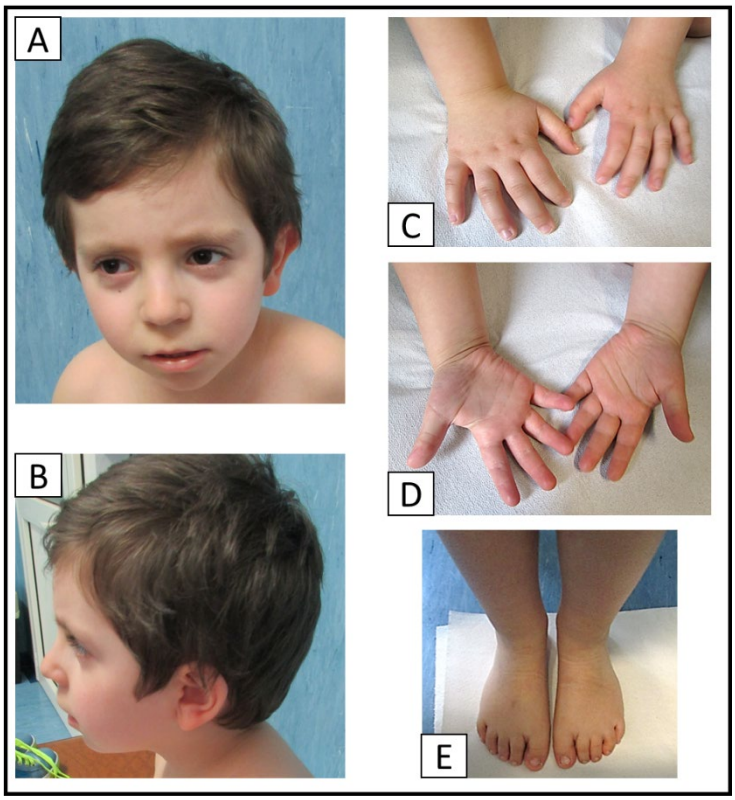

Figure 2. At our physical evaluation, our patient, affected by 9q21.13 microdeletion syndrome, presents upslanted palpebral fissure, hypertelorism, high palate, long philtrum, wide mouth, thin upper lip vermilion (A,B), clinodactyly of the 5th finger, short hands (C,D) and sandal gap (E).

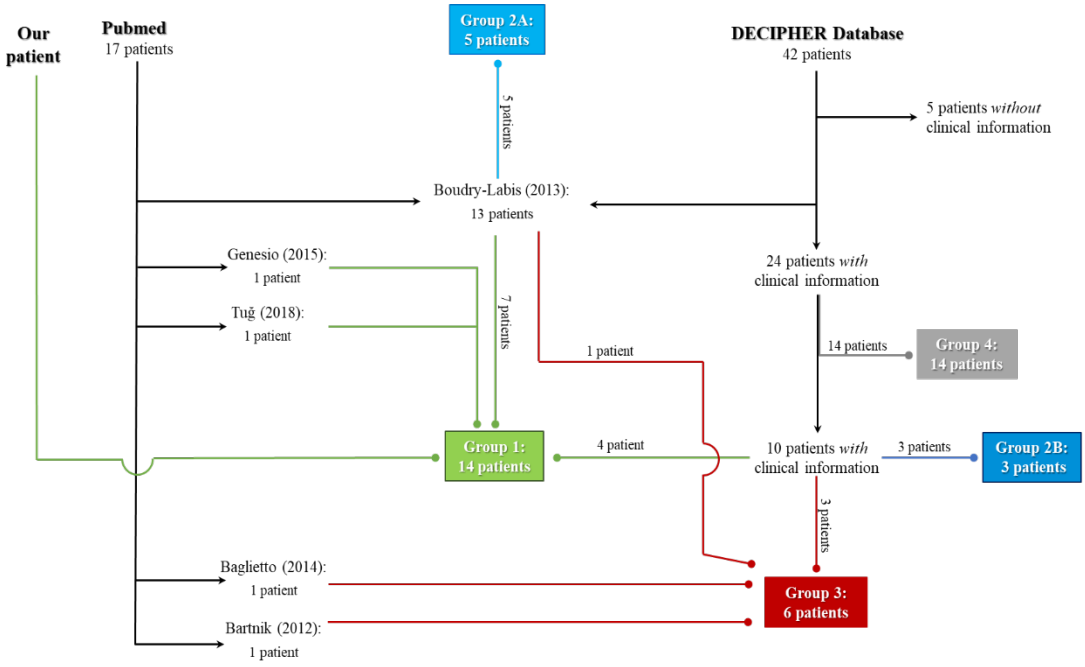

Figure 3. Workflow of literature and DECIPHER database search. Normal end arrow indicates where the patients come from (literature or DECIPHER database). The different color of oval end arrow indicates the belonging group of the patients. Arcs are present where there is a graphical intersection between the arrows.

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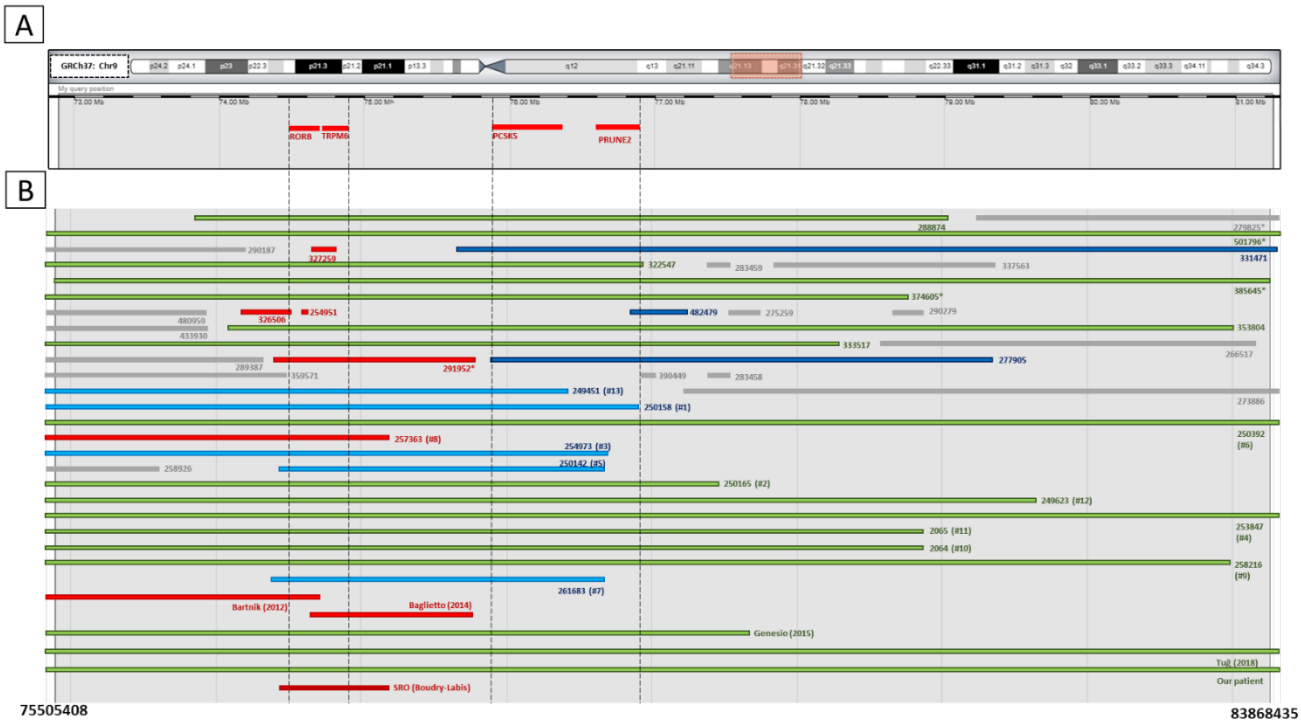

Figure 4. *Adapted from DECIPHER genome browser*. **A.** Schematic representation of main four genes (RORB, TRPM6, PCSK5, PRUNE) present in the de novo deletion on chromosome 9 of our patient; **B.** A total of 42 cases from DECIPHER genome browser with deletions localized or included in the locus 9q21.13q21.31 of interest. These 42 patients are divided into 5 groups and they are represented in different coloured bars:

- Group 1 (green) is composed of 14 patients, all share the deletion of our patient which involves at least the genes *RORB, TRPM6, PCSK5*, and *PRUNE2*. Thanks to this group, we explore the phenotypes related to very large deletions, which include other genes outside the four previous genes thought to be candidates for the phenotype of 9q21.13 microdeletion syndrome.

- Group 2 is composed of 8 patients, who have the 9q21.13 deletion, which involves in two different ways the genes *RORB, TRPM6, PCSK5*, and *PRUNE2*. This group can be divided in two other subgroups:

  - Group 2A (light blue) totally involves the genes *RORB* and *TRPM6* and partially the genes PCSK5 and PRUNE2. Through this group, we want to investigate the phenotypes related to haploinsufficiency of the main four genes of 9q21.13 micro-deletion syndrome.

  - Group 2B (dark blue) involves only deletions that include the genes *PCSK5* and *PRUNE2*. This subgroup is formed by 3 DECIPHER patients. We explore the phenotypes related to the deletions of these two genes in order to investigate their role as candidate genes for the neurological phenotype in 9q21.13 microdeletion syndrome.

- Group 3 (red) is composed of 6 patients who share a 9q21.13 deletion involving part and/or completely the genes *RORB* and *TRPM6*. Here, we investigate the phenotypes due to the haploinsufficiency of the main two genes involved in 9q21.13 microdeletion syndrome.

- Group 4 (grey) is composed of 14 Their deletions do not contain the four genes *RORB*, *TRPM6, PCSK5*, and *PRUNE2* and, obviously, the critical region of 9q21.13 micro-deletion syndrome. Hence, in our work, we do not consider the patients of this group because their interest is outside the aim of this article.

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Patients with 9q21.13 Microdeletion Syndrome		27 Patients (DECIPHER + Literature) Divided in Four Groups										Our Patient	28 Patients of Our Article	
		G. 1 (13 pt)	%	G. 2A (5 pt)	%	G. 2B (3 pt)	%	G. 3 (6 pt)	%	Total: 27 pt	%	G.1 (14th pt)	Total: 28 pt	%
	Sex:													
	Male	5/13	38.5	4/5	80	3/3	100	3/6	50	15/27	55.6	Male	16/28	57.1
	Female	5/13	38.5	0/5	0	0/3	0	3/6	50	8/27	29.6		8/28	28.6
	Unknown	3/13	23	1/5	20	0/3	0	0/6	0	4/27	14.8		4/28	14.3
	Karyotype:													
	Normal	8/13	62	3/5	60	3/3	100	6/6	100	20/27	74.1	Normal	21/28	75
	Altered	2/13	15	1/5	20	0/3	0	0/6	0	3/27	11.1		3/28	10.7
	Unknown	3/13	23	1/5	20	0/3	0	0/6	0	4/27	14.8		4/28	14.3
	Age at diagnosis													
	Minimum age	1y 10m		8y		1y		2y		1y		7y	1y	
	Maximum age	16y		16y		3y		15y		16y			16y	
Clinical and radiological findings	Intellectual disability (HP: 0001249)	13/13	100	5/5	100	1/3	33.3	5/6	83.3	24/27	88.9	+	25/28	89.3
	Global development delay (HP: 0001263)	9/13	69.2	5/5	100	0/3	0	1/6	16.7	15/27	55.6	+	16/25	57.1
	Autistic behaviour (HP: 0000729)	8/13	61.5	3/5	60	1/3	33.3	3/6	50	15/27	55.6	+	16/28	57.1
	Seizure (HP: 0001250)	6/13	46.2	4/5	80	0/3	0	3/6	50	13/27	48.1	+	14/28	50
	Hypotonia (HP: 0001252)	2/13	15.4	1/5	20	0/3	0	1/6	16.7	4/27	14.8	–	4/28	14.3
	Abnormal eye physiology (HP: 0012373)	5/13	38.5	1/5	20	0/3	0	2/6	33.3	8/27	29.6	+	9/28	32.1
	Brain anomalies (MRI brain) (HP: 0410263)	3/13	23.1	2/5	40	0/0	0	0/3	0	5/21	23.8	+	6/22	27.3
Dysmorphic features	Low anterior hairline (HP: 0000294)	2/7	28.6	0/4	0	0/0	0	2/2	100	4/13	30.8	–	4/14	28.6
	Hypertelorism (HP: 0000316)	2/7	28.6	1/4	25	0/0	0	2/2	100	5/13	38.5	+	6/14	42.9
	Upslanted palpebral fissure (HP: 0000582)	1/7	14.3	1/4	25	0/0	0	1/2	50	4/13	30.8	+	5/14	35.7
	High palate (HP:0000218)	3/7	42.9	0/4	0	0/0	0	1/2	50	5/13	38.5	+	6/14	42.9
	Long philtrum (HP: 0000343)	4/7	57.1	1/4	25	0/0	0	1/2	50	8/13	61.5	+	9/14	64.3
	Open mouth (HP: 0000194)	3/7	42.9	0/4	0	0/0	0	0/2	0	3/13	23.1	–	3/14	21.4
	Wide mouth (HP: 0000154)	2/7	28.6	1/4	25	0/0	0	0/2	0	4/13	30.8	+	5/14	35.7
	Thin upper lip vermilion (HP: 0000219)	3/7	42.9	3/4	75	0/0	0	1/2	50	7/13	53.8	+	8/14	57.1

Table 1. Clinical problems, radiological findings, and dysmorphic features of all 28 patients affected by 9q21.13 microdeletion syndrome. In the rows, they are divided into four groups and for each one, there are the frequencies of the indagated characteristics and their percentages. Then, we compare the 27 patients to our patient (grey column), and we recalculate the new percentages of the features of 9q21.13 microdeletion syndrome for the 28 patients (including our case).

"+" stands for clinical features of 9q21.13 microdeletion syndrome present in our patient. "–" stands for clinical features of 9q21.13 microdeletion syndrome not present in our patient. "G." means "Group". "%" refers to the percentages calculate on the basis of the frequencies. "y" stands for year(s). "m" stands for months. "pt" means patient(s). "HP" refers to human phenotypes.

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ID 70

Rare copy number variations in a romanian pediatric cohort with autism spectrum disorders

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Background: Autism spectrum disorders (ASDs) are complex, heterogeneous neurodevelopmental conditions (NDC) associated with lifelong challenges. ASDs have a strong genetic background characterized by a wide array of defects. In total, up to 30% of ASD individuals have a rare pathogenic defect, including rare copy number variants (CNVs), considered etiologic in 5-10% of patients, and rare sequence variants. For the rest of the patients, the genetic liability is still to be identified, warranting thus further research. Our paper summarizes the genomic findings in a Romanian pediatric cohort with ASDs, a population undercharacterized genetically in the scientific literature.

Methods: 305 children diagnosed with ASD were enrolled from the patients referred to the Prof. Dr. Alexandru Obregia Clinical Hospital of Psychiatry for various NDDs and neuropsychiatric problems, between September 2019 and February 2022. A control group comprising 300 age and sex matched neurotypically developing children was also assembled. Array-CGH was performed for both ASD and control groups on whole blood gDNA using 4x180K SurePrint G3 Human CGH microarray (Agilent Technologies). CNVs were labelled as rare and retained if they had a frequency <1% in the Database of Genomic Variants and occurred in <1% of the subjects in the total cohort. CNVs were further labelled as pathogenic, likely pathogenic or as variants of unknown significance (VUS) according to ACMG guidelines (2015). Genes overlapped by rare CNVs were analyzed and tested for enrichment against target gene lists extracted from the SFARI database.

Results: Array-CGH analysis detected 477 rare CNVs in the ASD group, with a mean number of 1.56 CNVs per patient. Rare CNV burden was significantly higher in the ASD group ($p<0.001$) and genes overlapped by rare exonic CNVs in the ASD cohort were enriched for syndromic and score 1 SFARI genes ($p<0.05$), as well as SFARI genes with scores 2 and 3 ($p<0.001$), compared to controls. Twenty-seven ASD individuals harbored rare clinically relevant genomic imbalances: one complex rearrangement (deletion/duplication), 7 duplications, 17 deletions and two Y-chromosome aneuploidies. Rare CNVs overlapping known ASD-associated CNV loci included duplications of 1q21.1, 15q11.2q13.1, 17p11.2, as well as deletions of 3q29 and 15q11.2. Dosage sensitive genes robustly associated with ASD and NDC, such as NRXN1, MBD5, and RORA, were also detected in our ASD group. Genes overlapped by VUS in the ASD group, which did not occur in the control group, included non-syndromic SFARI genes known to be intolerant to variation, such as ASTN2 and TM9SF4, as well as non-SFARI genes which are highly expressed in the brain, such as FOXK1, GNB5, UBASH3B, and RABEPK.

Conclusions: Our results highlight once more the genetic heterogeneity which underlies a wide array of pathogenic mechanisms in ASD. Array-CGH detection yield, expressed as the number of ASD patients with solved genetic etiology in our cohort, was 9%. Genomic results revealed significant enrichment for gene sets with well-established roles in ASD and NDC, thus making our ASD cohort a valuable resource for further search of genes with underrecognized involvement in ASD and NDC.

Funding: The research leading to these results has received funding from the EEA Grant 2014-2021, under the project contract No 6/2019.

ID 77

X-linked intellectual disability syndrome in female patient with mutation in HUWE1 gene

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Intellectual disability syndrome associated with mutations in the *HUWE1* gene with locus on the chromosome X includes global developmental delay with moderate or severe intellectual disability, no / poor speech development, dysmorphic features, mild skeletal defects, hypotonia and epilepsy (Moortgat et al., 2018). Here we present a 16-year-old girl with developmental delay, including no speech development, severe intellectual disability, drug-resistant epilepsy, microcephaly, dysmorphic features, atrial septal defect and submucosal cleft palate. Based on the tests performed chromosomal aberrations were excluded. Next-generation sequencing revealed the known molecular variant c.12469C>G, p.(Leu4157Val) in the *HUWE1* gene, which was previously described in other patients with syndromic intellectual disability. Carrier tests in the patient's parents suggest that the above-mentioned molecular variant occurs *de novo*. Detailed analysis of the patient's phenotype showed its consistency with previously described one, seen in other patients with mutations in the *HUWE1* gene. *De novo* mutations in the *HUWE1* gene in women are often associated with the full-blown course of the disease. In familial cases carrier women may have mild cognitive problems and dysmorphic features, while severe course of the disease is observed in men. Chromosome X inactivation test in our patient showed its non-random inactivation (97:3). Assuming that the same inactivation pattern applies to all tissues and that the chromosome with the normal copy of the *HUWE1* gene is inactivated, it could additionally explain the symptomatic course of the disease in this patient.

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- abstracts -

ID 14

A new French network for challenging behaviors with genetic origin : the GenoPsy Network

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On the eve of the 4th National Plan for Rare Diseases (PNMR), a new network will be set up in France to provide personalised support for people with a rare genetic disease associated with behavioural disorders or even "challenging behaviours".

To achieve this, a network of centres has been set up throughout France, under the name « GénoPsy network ». It will comprise 5 Rare Disease Reference Centres (Dijon, Clermont-Ferrand, Paris Sainte Anne, Rouen and Lyon) and 6 Rare Disease Competence Centres (Rennes, Nantes, Poitiers, Bordeaux, Paris Créteil and Paris Necker).

The missions of the GénoPsy network are threefold: (i) to offer specialised advice on behavioural disorders in order to guarantee personalised medicine, (ii) to offer a range of 'rare diseases and psychiatry' training courses for all professionals in the region, and (iii) to play a role in research in order to advance knowledge of rare diseases in the field of psychiatry. Each CRMR and CCMR will develop its own theme: immuno-inflammation, psycho-social rehabilitation, psychopharmacology, neuromodulation, molecular genetics and 'orphan' prescriptions.

Finally, the strength of the GénoPsy network lies in its cross-disciplinary approach and its close collaboration with families, carers and the people affected, with the aim of creating a participatory network.

Mots-clés : GénoPsy, réseau, maladies rares, génétique, psychiatrie, pluridisciplinaire, participatif, comportements défis, syndromes génétiques

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ID 35

A LONGITUDINAL STUDY OF CHALLENGING BEHAVOUR AND AUTISTIC SYMPTOMS IN SMITH-MAGENIS' SYNDROME

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We will present data from a prospective longitudinal study of challenging behavior autistic symptoms in a cohort of individuals with Smith-Magenis' syndrome (SMS). The prevalence of challenging and disruptive behaviors is high in SMS, including self-injurious behaviors, hyperactivity, aggression, and tantrums. Autistic symptoms are common. Several studies have found that individuals with SMS are significantly more likely to show disruptive or aggressive behavior than individuals with other genetic syndromes and individuals with ID. Less is known about how these difficulties progress over time. In this study, we have assessed challenging behavior and autistic symptoms in 28 participant with SMS from Norway and Sweden. Challenging behavior was assessed by using the Developmental Behaviour Checklist (DBC), autism symptomatology was assessed by using Sensory Responsiveness Scale (SRS) and Social Communication Questionnaire (SCQ). The first assessment was conducted in 2015-16. We are now in the process of repeating the assessments in the same cohort.

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ID 36

Psyciatric symptoms in the Norwegian smith-magenis' and potocki-lupski syndrome population

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We will present data on the prevalence of psychiatric symptoms in a Norwegian cohort with Smith-Magenis' (SMS) and Potocki-Lupski syndrome (PTLS). There is little research on the psychopathology in SMS and PTLS, although we know the prevalence of psychiatric disorders is high the population with intellectual disability and autism spectrum disorders. There has been suggested a high comorbidity with anxiety and depression in SMS, this is yet to be studied. Anxiety is described in children with PTLS, but there is very little knowledge about the severity of symptoms in adult life. We are investigating the prevalence of psychiatric symptoms in the Norwegian SMS and PTLS populations. We are assessing the prevalence of symptoms using the Psychopathology in Autism Checklist. To date we have included approximately 15 participants with SMS and 10 with PTLS. We aim to include more participants. We hypothesis that there is a high prevalence of psychiatric symptoms in the SMS and PTLS populations. Further knowledge may help assesses the risk of mental health issues, which may be overlooking due to behavior difficulties associated with the syndromes. Further knowledge may also be important for choice of treatment and can potentially lead to interventions that are more accurate. This project is part of the BUPGEN project, a large national biobank and heath register run by the K.G. Jebsen Center for Neurodevelopmental Disorders.

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ID 47

Prioritizing for impact: Establishing criteria to select new ERN-ITHACA clinical practice guideline topics

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Introduction: Clinical practice guidelines (CPG) may help to meet information needs and improve healthcare for individuals with rare genetic neurodevelopmental disorders. Considering the wide range of conditions and associated health problems covered by European Reference Network ITHACA (Intellectual disability, TeleHealth, Autism and Congenital Anomalies), as well as the significant resources required for guideline development, it is important to prioritize those guideline topics of highest relevance. We aim to develop prioritization criteria for the selection of new guideline topics, involving all relevant stakeholders (patient representatives, clinicians, and allied healthcare professionals, amongst others).

Methods: ERN-ITHACA develops guidelines for both specific (genetic) conditions and shared health problems. Initial sets of prioritization criteria for both types of guidelines were developed based on an existing systematic review of the literature, the ERN CPG Methodological Handbooks, and discussions at the 2022 ERN-ITHACA Board Meeting. The criteria were edited based on internal feedback from the ERN-ITHACA Executive Committee and Patient Advisory Board. Currently, all stakeholders are invited to rate the importance of these criteria and propose relevant guideline topics through an openly available survey. The prioritization criteria will be refined and confirmed through a final survey round and consensus meeting with a panel of representatives from all stakeholder groups.

Results: Prioritization criteria will be available at the time of the EuroNDD meeting in April.

Discussion: Through this consensus-building approach, ERN-ITHACA aims to develop a guideline prioritization strategy that is democratic, transparent, and ensures the relevance of its guideline development efforts to healthcare professionals and affected individuals and families.

ERN ITHACA Grant References: EU4Health Grant Agreement nr. 101085231.

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ID 48

'We are the engine': Patient advocate perspectives on clinical practice guideline development for rare congenital malformations and/or intellectual disability

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Introduction: People living with rare congenital malformations and/or intellectual disability often struggle to access adequate healthcare. Clinical practice guidelines can help to ensure evidence-based care; yet, developing guidelines for these rare conditions proves complex in which perspectives of affected individuals and families have received little attention.

Methods: Focus groups were organized to discuss guideline use and development with European patient advocates involved in European Reference Network ITHACA (Intellectual disability, TeleHealth, Autism and Congenital Anomalies).

Results: Patient advocates considered guidelines important to meet information and care needs and to support their advocacy efforts. Important guideline characteristics included representing the heterogeneity within conditions; holistic approaches; user-friendliness for affected individuals and families; and reliability of the provided information. They described guideline development and implementation as challenging, iterative processes requiring effective partnership between clinicians, patient advocates, and other stakeholders.

Discussion: Understanding the perspectives of patient advocates is essential to develop guidelines that meet needs of affected individuals and families. Challenges identified in this study included balancing urgent information needs with lengthy development processes and integrating scientific and experiential knowledge within guidelines.

ERN ITHACA Grant References: EU4Health Grant Agreement nr. 101085231

ID 51

What matters most? A mixed-method study to develop a core patient reported outcome set for individuals with genetic intellectual disability

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Background: In order to improve quality of care and research for individuals with genetic intellectual disability (GID), it is essential to measure patient reported outcomes (PROs). PROs represent patient perspective on their health. Unfortunately, various and potentially irrelevant PROs are measured for individuals with GID. Therefore, the aim of this study was to identify most relevant PROs for individuals with GID and develop a generic core PRO set.

Methods: First, we identified PROs though a comprehensive literature review and focus groups and interviews with individuals with GID, caregivers, and experts (healthcare professionals and European patient representatives). PROs were integrated and operationalized within a conceptual framework with an expert group: the pilot generic core PRO set. The upcoming months the pilot generic core PRO set will be presented in a two-round Delphi survey with individuals with GID, caregivers, and experts in which participants rate the importance of the PROs. The Delphi survey will be followed by one face-to-face consensus meeting with individuals with GID and caregivers and one online consensus meeting with experts to reach consensus on the final generic core PRO set.

Results: Results of the Delphi survey and the two consensus meetings will be presented at the conference.

Discussion: Through this project, we will reach an important milestone in meeting the needs of individuals with GID by identifying most relevant PROs and developing a generic core PRO set for the whole GID population. The next step involves selecting suitable patient reported outcome measures (PROMs), which are standardized questionnaires completed by the patient or a proxy (i.e. caregiver) to adequately measure these PROs: the generic core PROM set. Eventually, by implementing the generic core PROM set, we hope to improve quality of care and research for the complex and vulnerable population with GID.

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ID 78

Integrated care for patients with NDD and rare diseases in Romania

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Background/Objectives: With a huge diversity of over 6000 rare diseases, the delay in diagnosis, misdiagnosis and lack of early intervention or absence of treatment continue to impact rare diseases families all over the world.

In Romania live, according to international statistics more than 1.000.000 patients with rare diseases, the majority being invisible for the healthcare system, due to lack of a national program for genetic testing for rare diseases, only 3 diseases in newborn screening and the use of ICD10, which cover less then 10% of the rare diseases.

Since 2014 Romanian Ministry of Health has declared rare diseases as a public health priority, many progresses have been registered because of patient's advocacy, like National Plan for Rare Diseases or accreditation of Centers of Expertise. Still the country has an old care infrastructure, not enough medical experts because of migration of the qualified work force, and political instability.

In response, Romanian Prader Willi Association has established in 2011 through a Norwegian grant NoRo Center, a pilot reference center for rare diseases to reduce the burden of the disease for families, children and young adults affected with rare diseases with intellectual and developmental disabilities, at NoRo Center in Romania.

Most of the NoRo beneficiaries have diseases with a genetic origin, polyhandicap, and/ or NDD and their problems fall into several categories: motor, cognitive, seizures, nutrition restrictions, psycho-social challenges, behavioral or sleep problems. They have also difficulties in getting their rights and assessment of their disabilities and finding the right services at the right time. All these needs were considered in the development of our services.

Methodology:

- ✓ Creating an interdisciplinary approach for children and young adults affected with rare diseases with intellectual and developmental disabilities at NoRo Center in Romania.
- ✓ Implementing quality standards in our services.
- ✓ Monitoring system for patients care.
- ✓ Collaboration with all Centers of Expertise to ensure continuity of care through network collaboration; Establishing RO.NMCA-ID and becoming full members of ITHACA in 2017.
- ✓ Collaboration with medical experts to ensure continuity of care by establishing community support networks, collaboration with schools, training community nurses, family doctors and sanitary mediators on case management for RDs.
- ✓ Development of innovative approaches supporting patient pathways, to reduce the waiting time for vulnerable groups of rare diseases and disabled people to get the diagnosis, proper care and services.

Results: More than 2500 beneficiaries of our services since opening the center, 854 community nurses, 50 sanitary mediators, and 850 doctors trained in case management for rare diseases in the last 3 years and more than 3000 patients coordinated to services through HelpLine NoRo since 2011. Generally, our beneficiaries indicated a high level of satisfaction with the service received and felt that it met its objectives.

Conclusion: NoRo Centre piloted an innovative and successful integrated care approach in a challenging health care environment using Frambu center as a model, adapting it to the local and national context. Although there is room for further improvement, our beneficiaries reported high satisfaction with the care services received and our training sessions on case management opened new and effective avenues towards increasing our patient-clinician collaboration at national and international level.

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Navigating neurodevelopmental disorders: Insights from a romanian cohort and empowering patients through education

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Acknowledgements: The Ro-NMCA-ID (RoNetwork Multiple Congenital Abnormalities with ID) Group: Maria Puiu, Adela Chirita-Emandi, Dorica Dan, Andrada Gheorghe, Lacramioara Butnariu, Oana Iuhas, Kinga Kozma, Marius Bembea, Aritina Morosanu, Carmen Niculescu, Cristina Rusu, Monica Panzaru, Claudia-Maria Jurca, Ioana Streață, Anca-Lelia Riza, Monica-Laura Cara, Mihai-Gabriel Cucu, Eugenia Roza, Oana Aurelia Vladâcenco, Diana Epure, Raluca Ioana Teleanu, Amelia-Mihaela Dobrescu, Florin Burada, Mihai Ioana. CExBR Pediatric Neurology Obregia (Pediatric Neurology Rare Disease Expertise Center Obregia) Group: Alice Dica, Carmen Sandu, Cristina Anghelescu, Cristina Haritina Motoescu, Cristina Pomeran, Dana Surlica, Ioana Minciu, Oana Tarta-Arsene, Catrinel Iliescu, Diana Barca, Niculina Butoianu, Carmen Burloiu, Magdalena Budișteanu, Dana Craiu. CExBR Pediatric Neurology "V. Gomoiu" Hospital (Center for Expertise in Rare Diseases in Pediatric Neurology, Pediatric Neurology Clinical Department, Children's Clinical Hospital "Dr. Victor Gomoiu" Bucharest) Group: Eugenia Roza, Oana Aurelia Vladâcenco, Diana Epure, Raluca Ioana Teleanu.

Background: With 1-3 % of people worldwide diagnosed with Neurodevelopmental Disorders (ND), including conditions like Autism Spectrum Disorders (ASD), Intellectual Disability (ID), and/or Global Developmental Delay (GDD), this abstract sheds light on a Romanian cohort's experiences within this complex domain. The abstract also aims to tackle issues of patient education such as managing the Psycho-Social implications in the personal life and within Society.

Methods and Results: Between 2015–2022, 371 patients from various regions of Romania with global developmental delay (GDD) and/or intellectual disability (ID) were referred to the Regional Centre for Medical Genetics Dolj (CRGM Dolj) for genetic testing. Consistent with data seen in the literature, the study reported the diagnosis rate for chromosome microarray analysis (CMA) of 21.29%. We characterized the pCNV yields and profiles in a Romanian patient cohort presenting unexplained GDD/ID alongside distinct features, contextualizing our findings within the framework of other European studies.

We also highlight ways in which CRGM Dolj has included patient education as part of the general genetic counselling as well as in awareness campaigns organized in collaboration with Craiova Medical Students' Society,and patients advocacy groups.

Conclusions: To conclude, a diagnosis of a Neurodevelopmental Disorder (ND) can have a significant impact on patients and their families. It is important to bring forward study findings which fill the diagnostic gap, as well as tackle issues of patient education and the psycho-social aspects associated with these disorders, advocating for personalized strategies to enhance overall intervention effectiveness.

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ID 17

Towards precision medicine: Challenges and advancements

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The diagnostic approaches for monogenetic neurodevelopmental disorders (mNDDs) have transitioned from the phenotype-first to a genotype-first approach. Ongoing developments in techniques and artificial intelligence are bringing us closer to the realization of genetic therapies and precision medicine.

To assess treatment efficacy, there is a need for prognostic, predictive, and responsive biomarkers. However, the current emphasis on molecular genetics over comprehensive clinical data collection has led to a gap in our understanding of the natural history and pathogenesis associated with mNDDs. As a consequence, we face challenges in the identification of potential treatment targets.

Responsive biomarkers for mNDDs have not yet been identified. However, over 800 biomarkers are investigated in multiple studies as recently was shown for autism spectrum disorders (ASD) [1]. The substantial heterogeneity in ASD and the extensive variability of these biomarkers, both within and between individuals, is the main challenge in biomarker research [1]. Small sample sizes, inadequate correction for multiple testing, and the absence of a replication cohort have led to overfitting [1].

To overcome challenges, it is essential to have a comprehensive understanding of clinical genetics. Clinical outcome measures are crucial in guiding the selection of precise endpoints. Clearly defined clinical endpoints are essential in the translation of preclinical studies to the patient. This approach leads to an understanding of the underlying pathogenesis of mNDDs and, ultimately, the identification of specific treatment targets.

To illustrate comprehensive phenotyping, we studied growth, body composition, and endocrine-metabolic profiles in individuals with Kleefstra syndrome (*Figure 1)*. This study emphasizes the potential of clinical outcomes in the translation of preclinical studies and in the identification of biomarkers. Furthermore, we integrate clinical outcomes with IPSC-based data collections within the BRAINmodel consortium (*Figure 2)*. By focusing on an individual patient with a NDD due to a monogenetic cause, we address challenges and advance towards precision medicine.

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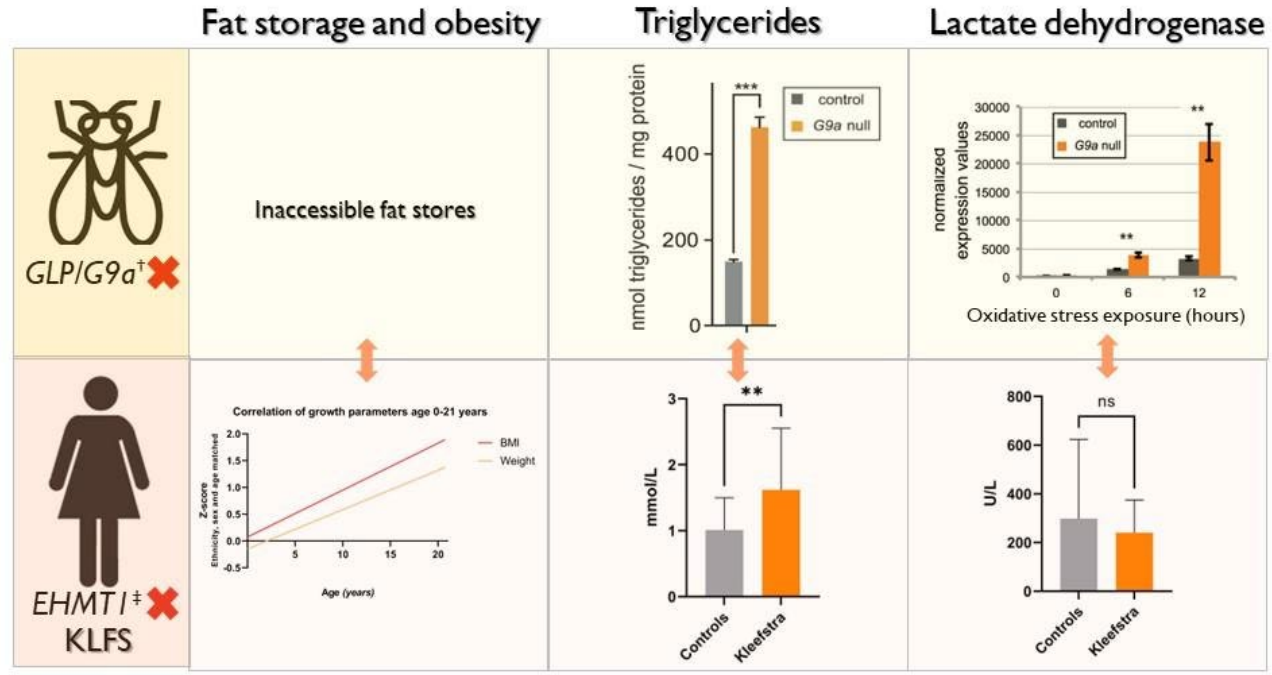

† Riahi, 2019. The histone methyltransferase G9a regulates tolerance to oxidative stress–induced energy consumption.
‡ Bouman et al. 2023. Growth, body composition, and endocrine-metabolic profiles of individuals with Kleefstra syndrome provide directions for clinical management and translational studies. (Accepted.)

Figure 1. Understanding clinical outcomes is the first step in the identification of biomarkers, as it enables the translation of preclinical studies (Riahi et al., 2019).

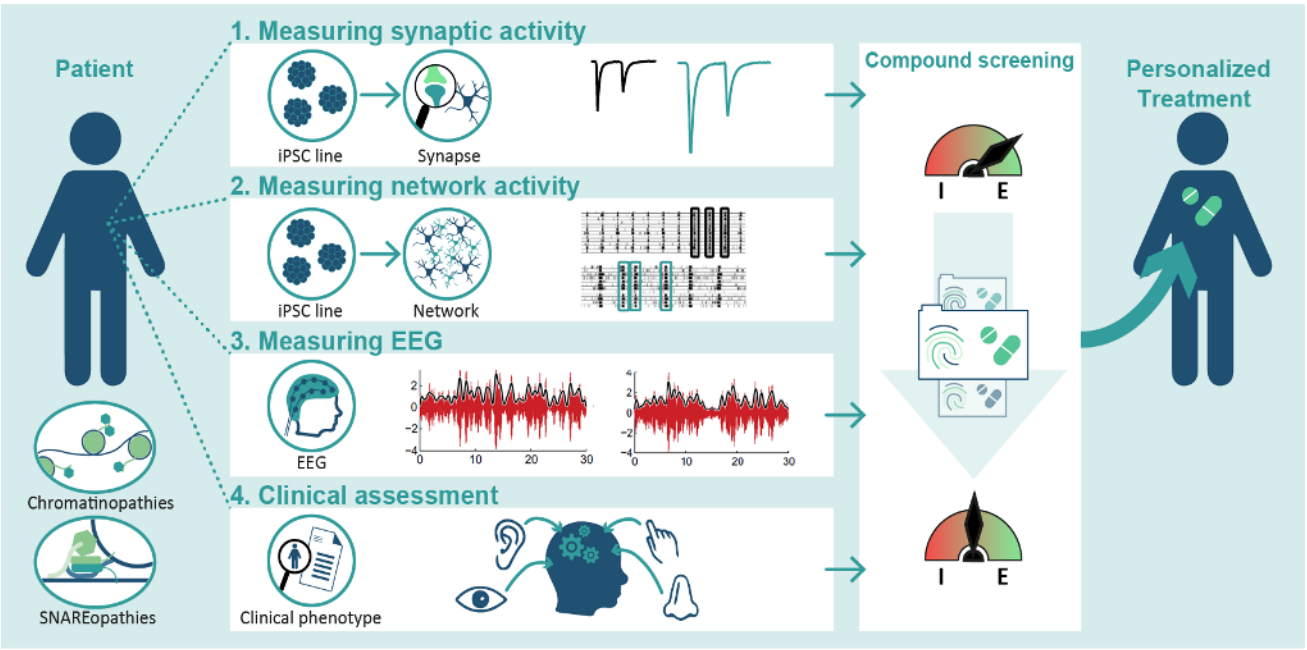

Figure 2. BRAINmodel strategy to identify biomarkers for mNDDs.

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ID 37

Eating behaviour and issues in rare genetic disorders

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Reports of adverse eating behaviour is numerous amongst children with rare genetic disorders. This behaviour is often challenging for their next of kin and caregivers. However, systematic mapping of this is lacking. Adverse eating behaviour may cause severe weight loss, nutritional deficiency supplement dependence and psychosocial importance. Thus, knowledge about eating behaviour in rare genetic disorders is important in order to implement interventions. Interventions will vary based on the type, cause and topography of the eating behaviour.

The overall aim of this project is to map eating behaviour in rare genetic disorders, to broaden the knowledge on eating issues and identify rare genetic disorders for further in-depth investigation on eating behaviour.

Within rare genetic conditions, several have been identified as risk factors not only for neurodevelopmental disorders but also for obesity. For instance, the 16p11.2 proximal deletion and Smith-Magenis syndrome (the 17p11.2 CNV) are recognised as very penetrant risk factors for obesity. In parallel, individuals with Smith-Mageni (17p11.2 deletion) display interesting eating habits. Interestingly, in the reciprocal CNVs, the 16p11.2 duplication carriers are often leaner and babies with 17p11.2 duplication (reciprocal to Potocki-Lupski syndrome) often experience failure to thrive and the individuals with this syndrome tend to weigh less than their peers. Thus, for these copy number variants, we observe a dose response for weight/BMI per copy of the deleted/duplicated region. These “mirror” phenotypes observed for some genomic loci, highlight that genes within these neuro-susceptibility loci are playing a key role in regulation of eating and weight. This evidence highlights the phenotypic and genetic overlap between neurodevelopmental conditions and extreme weight outcomes.

We hypothesize that there are differences in eating behaviour in the different subgroups which may partially contribute to the weight differences observed in individuals with rare genetic syndromes. We also hypothesize that the eating behaviour will be opposite in reciprocal (i.e. deletion versus duplication) CNVs.

We will present results from the comparison of the eating behavioural profile based on the CEBQ questionnaire for individuals with rare genetic syndromes. We will specifically target the rare genetic disorders, 16p11.2 proximal and distal and 17p11.2 CNVs, through the PARDI-AR questionnaire which assesses ARFID symptomatology across domains including lack of interest/appetite, fear of aversive consequences of eating, and sensory based avoidance. Finally, we will correlate this with their weight, height and BMI-profiles, to investigate behavioural drivers of extreme BMI outcomes.

This new knowledge may help to pave the path for choice of interventions in individuals with severe outcome from adverse eating behaviour.

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ID 45

Individualized antisense oligonucleotide therapies for patients with rare neurological disorders

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Antisense oligonucleotides (ASOs) offer the potential to treat patients with genetic diseases. For tissues allowing local injection, such as the brain, spinal cord, and eye, proof-of-concept has been shown for example in spinal muscular atrophy and Leber congenital amaurosis. ASOs can also benefit patients with rare pathogenic variants, as evidenced by the development of custom-made and locally delivered ASOs like Milasen and Atipeksen. This underlines the potential of ASOs as individualized medicines, specifically for very small groups of patients, where the group size can be as low as a single individual. However, there usually is no incentive for pharmaceutical companies to develop such approaches, due to the extreme rarity of these variants.

In 2020, the Dutch Center of RNA Therapeutics (DCRT) was founded; a collaboration of Dutch academic centers with a track record in ASO development aiming to provide genetic therapies for patients with nano-rare variants and to offer these treatments in a not-for-profit manner. Shortly after, the N=1 Collaborative (N1C, global) and the 1mutation1medicine (1M1M, European) initiatives were founded. These initiatives are aiming at standardizing and optimizing the development of n=1+ ASO treatments, and to provide processes for the assessment of eligibility, clinical implementation of treatment, and monitoring of patients for safety and efficacy. To this date, we have created a framework for selecting suitable candidate patients and variants, established guidelines and a pipeline for the pre-clinical development of ASOs, and are actively working on improving screening for neurotoxicity in newly generated *in vitro* platforms.

Here, we present an overview of our international initiatives and the work we do. We show how we are selecting promising candidates for the individualized treatments as well as the workflow towards clinical implementation.

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ID 56

Cognition and emotion in noonan syndrome: Current insights into diagnostics and treatment

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Introduction: Individuals with Noonan Syndrome Spectrum Disorders (NSSD) may have to deal with various cognitive and psychological challenges throughout their life. We will present an overview of current insights into strengths and weaknesses in information processing and social-emotional functioning of adult patients with NSSD. Additionally, we will share the results of a study on feasibility and effectiveness of the Social-Emotional training for adults with NSSD (eSENS), an eHealth intervention developed to enhance social cognitive skills.

Methods: Cognitive characteristics and common symptoms of psychopathology are summarized based on a literature review (Wingbermühle et al., 2022). The eSENS training, designed using evidence-based elements from social cognition training in individuals with other neurodevelopmental disorders, was evaluated for a group of 12 adults (age range 20-41). They completed questionnaires regarding social cognition and overall wellbeing before and after the training, as well as a weekly questionnaire about emotion regulation. The results were analyzed using non-parametric tests.

Results: Intelligence levels in adults with NSSD are variable but generally slightly diminished, with corresponding abilities in most other specific cognitive domains. Social cognition can be considered suboptimal (alexithymia and problems in mentalizing), and internalizing behavioral problems appear to occur more frequently. The eSENS study demonstrated significant improvement on measures of alexithymia (p= .01), emotion regulation (reappraisal, p= .01; suppression, p= .01), anxiety levels (p= .01), and experienced self-efficacy (p= .03). Evaluations of training partners (family members, partners or friends of the patients) involved in the training supported these significant findings.

Conclusions: Based on the presented results, recommendations will be made for diagnostic and treatment purposes in clinical practice. Given the substantial variability in cognitive and emotional functioning in NSSD, referral for individual neuropsychological assessment is essential to provide appropriate advice. In cases of social emotional problems, eSENS seems to be a viable eHealth intervention for adults with NSSD.

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ID 96

A 16-months old baby with ADNP syndrome: when a very early assessment allows a preventive transdisciplinary work

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Background: Recently described in 2014, the activity-dependent neuroprotective protein (ADNP) syndrome combines a neurodevelopmental delay (intellectual disability and/or autism) with multiple body organ involvements. This syndrome is caused by a single de novo mutation. Our recent literature review concluded that management requires close collaboration between physicians and psychiatrists, and that improvements may be achieved over time when intensive multidimensional and integrative care is provided.

Case Presentation: We report the case of a female baby diagnosed at 16 months of life. Genomic sequencing was launched because of a strong axial hypotonia first observed when the child was hospitalized at 4 months for a severe bronchiolitis. Physical therapy was provided weekly, first for her respiration and then from 12 months on for her motricity; weekly psychomotricity began at 8 months, and speech therapist's assessment was made at 13 months for chewing difficulties. However, the family also worried about a relational withdrawal, and that the baby sometimes was absorbed by looking at her hands. This assessment revealed some delay in communicational abilities and a lack of initiation in interaction, so that weekly speech therapy sessions began to support communicative skills. Finally, when the ADNP diagnosis was made, the family solicited our pedo-psychiatric team. As we met them, the child was already progressing in motor and interactive abilities, with very good moment of joint attention and real 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 were particularly attentive to this parental feeling and decided not only to complete the developmental assessment, but also, without waiting, to complete the multi-disciplinary care with a support of parent-child interaction specifically designed for children at-risk of ASD.

Discussion: By a very early and intensive intervention, we hope to be able 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. This case highlights the interest of an early genome sequencing when warning signals are present.

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

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- abstracts -

ID 1

De novo variant in TLK2: Clinical evaluation and genotype-phenotype of a neurodevelopmental disorder

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We report the case of a 22- year -old woman, followed for genetics, psychiatry and neurologist due to intellectual disability, dysmorphic symptoms and attention deficit hyperactivity disorder. She was born of non-consanguineous parents. No history of intellectual disability or neurological diseases. Two healthy male brothers aged 29 and 26. She was delivery at 38 weeks without complications. Weight 2.400 gr, T: 44 cm and PC 31 cm. Delay in acquiring developmental milestones.

Examination at 22-yo showed peculiar fascies, microcephaly, broad forehead, hypertelorism. Palpebral fissures short, oblique upwards. Bilateral epicanthal folds, ears of low implantation. Large nose with bulbous tip, small mouth, with thin lips, macroglossia, broad lower jaw, short and flat philtrum, prognathism and high palate.

Throughout years, extensive investigations were performed, metabolic studies and skeletal series were normal. CT, MRI and MR angio 2002 it has a ventricular size in high limits. 2nd MRI and MR angio 2005 moderate dilation of the ventricular system, in the same, which may be significant for some subcortical atrophy.

Karyotype 46 XX - X-fragile: negative. Most common microdeletion syndromes (MLPA) : normal.Molecular study to detect microdeletion in region 22q11.2 : normal.Smith-Magenis SD and congenital central hypoventilation syndrome: negative

FISH: no deletion of subtelomeric regions.
Array-CGH 60 Kb : Normal
High resolution karyotype 46XX
Microarray CGH 1000K arr 8p23.3 1,504-084-1,509,519 x1 female karyotype with microdeletion in 8p23.3 de novo.
Study of family segregation: negative.
Whole exome sequencing detected LP heterozygous variant p. Arg546Gly in the TLK2 gene.

The variant found p.Arg546Gly is not found in the databases of general population consulted. It has not been described in the scientific literature or classified in databases of genetic variants of clinical relevance. Predictors indicate a deleterious effect on the protein encoded by this gene. This variant is in a functionally relevant domain of the protein involving a hot spot. TLK2 is a protein-coding gene. It encodes a nuclear serine/threonine kinase. The encoded protein functions in regulating chromatin assembly in the S phase of the cell cycle by regulating the levels of a histone H3/H4 chaperone. Associated with repairing double-stranded breaks of DNA damage caused by radiation.

Associated diseases include autosomal dominant intellectual developmental disorder 57. Among its related pathways are the regulation of miRNA, the response to DNA damage and the regulation of Chks at checkpoints.

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ID 2

A RECURRENT DE NOVO MUTATION IN *ZMYND11* ASSOCIATED WITH GLOBAL DEVELOPMENTAL DELAY GENOCOPY THE 10p15.3 DELETION SYNDROME: A CASE REPORT .

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Background/Objectives:

A 7-year-old patient initially diagnosed with Silver-Russel syndrome due to mosaicism of chromosome 7 returns to our genetic consultation for diagnostic re-evaluation. Characteristics symptoms are global developmental delay (84%), hypotonia, feeding difficulties, short stature and several facial dysmorphisms (microcephaly, depressed nasal bridge and micro retrognathia).

Methods:

Karyotype and CGH array were performed. MLPA assay (MS-MLPA Probemix ME032 DUP7-DUP14) was also done to test if there was maternal uniparental disomy of chromosome 7 (DUP7). Clinical exome was sequenced by Human Whole-Genome Sequencing with the Nextera™-DNA-Flex-Library Preparation Kit (Illumina).

Results:

Karyotype and CGH array were normal. MLPA assay revealed absence of DUP7. The analysis of the clinical exome showed a heterozygous autosomal dominant missense variant: c.1798C>T p.(Arg600Trp) in *ZMYND11* (NM_006624.5), classified according the ACMG guidelines as pathogenic. Genetic testing of both parents showed it had arisen *de novo*.

Conclusion:

Zinc finger MYND-type, expressed in many human tissues, acts as a transcriptional repressor, playing an inhibitory role in the muscle and neuronal differentiation steps. Specifically, the mutated position in this case Arg600 is very conserved and essential for its binding to ligands (Kateb et al.,2013). *ZMYND11* has also been proposed as a candidate gene for 10p15.3 microdeletion syndrome, which shares common clinical features with our patient (DeScipio, 2021). Moreover, other authors have described the same mutation (Cobben,2014), so that it can be considered as definitely pathogenic. Finally, the same SNP has been reported 4 times in Decipher and 8 times in ClinVar thus the variant here reported could be a *hotspot* mutation.

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ID 3

Exploring the mild phenotype of KCNC1 variants beyond myoclonic epilepsy: A case report

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The gene *KCNC1* encodes for the protein Kv3.1, a voltage-dependent potassium channel found in neuronal cells. Genetic variations in *KCNC1* have been implicated in numerous neurological conditions, such as epilepsy, ataxia, or migraines (PMCID: PMC6649617). In the most severe end of the spectrum, pathogenic variants in this gene are associated to a specific form of progressive myoclonic epilepsy (MIM #616187). This disorder typically emerges in the first years of life with a progressive course, often accompanied by impairments in neurodevelopment, motor coordination, and sensory function. It commonly arises as a *de novo* mutation, and most of the patients become wheelchair-bound during adolescence. Here, we described the case of 12-year-old boy that was referred to our appointment due to moderate intellectual disability, attention deficit hyperactivity disorder, and non-progressive epilepsy. No relevant family history or parental consanguinity were known. On physical examination, we noticed macrocephaly, thick and broad eyebrows, wide chin and synophrys. Previous investigations, including brain magnetic resonance imaging, echocardiogram, and chromosomal microarray and *FMR1* analysis, were normal. Electroencephalogram detected paroxysmal activity in the form of sharp and slow waves in the rolandic-temporal areas of the left hemisphere. We decided to perform clinical exome sequencing who identified the heterozygous variant NM_001112741.2:c.1015C>T, p.(Arg339*), in the gene *KCNC1*. Segregation studies conducted in the parents confirmed this variant to be de novo. In a recent case report, the same variant was already described in one family, where affected members (the father and two sons) exhibited intellectual developmental impairment and characteristic facial dysmorphisms, with no documented history of seizure episodes or epilepsy (PMID: 28145425). With this report, we hope to expand the known *KCNC1*-related phenotype and to improve clinicians' recognition of this disease.

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ID 26

Developing a novel genotype-to-phenotype prediction tool for chromosome deletions – the chromosome 6 project

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Introduction: Information on the clinical consequences of rare chromosome aberrations is often limited, posing challenges for both patients and their families. The Chromosome 6 Project (C6P) aims to empower parents of children with a structural chromosome 6 aberration by providing them with reliable information on the expected phenotypes of their child. To achieve this, C6P collects phenotype and genotype data directly from parents and combines it with data from literature reports. In the current study, we developed Del2Phen, a software tool that uses the collected data to produce deletion-specific phenotype information for all chromosome 6 deletions.

Methods: Del2Phen was developed to produce a phenotype description for a patient based on clinical features observed in a group of patients with similar deletions (Figure 1). Similar deletions are defined using pre-set parameters, based on the clinical effect and predicted haploinsufficiency (HI) effect of the involved genes. In this study, we assessed which parameter settings result in sufficiently large groups of genotypically similar individuals and accurate phenotype predictions.

Results: Del2Phen produces an accurate phenotype prediction when deletions are grouped using both of the following parameters: (i) concordance in the involvement of genes known to have a highly penetrant phenotypic effect and (ii) at least 80% overlap in HI-gene content. In groups that exceed a certain size, the minimum HI-gene overlap can be increased, provided that groups remain large enough for a reliable phenotype prediction.

Conclusion: We developed a novel phenotype prediction tool that uses parent-derived data to provide deletion-specific phenotypic information directly to parents. Although Del2Phen was developed for chromosome 6, it can be adjusted for use in other chromosomes, thereby addressing the information needs of parents of children with anychromosome deletion.

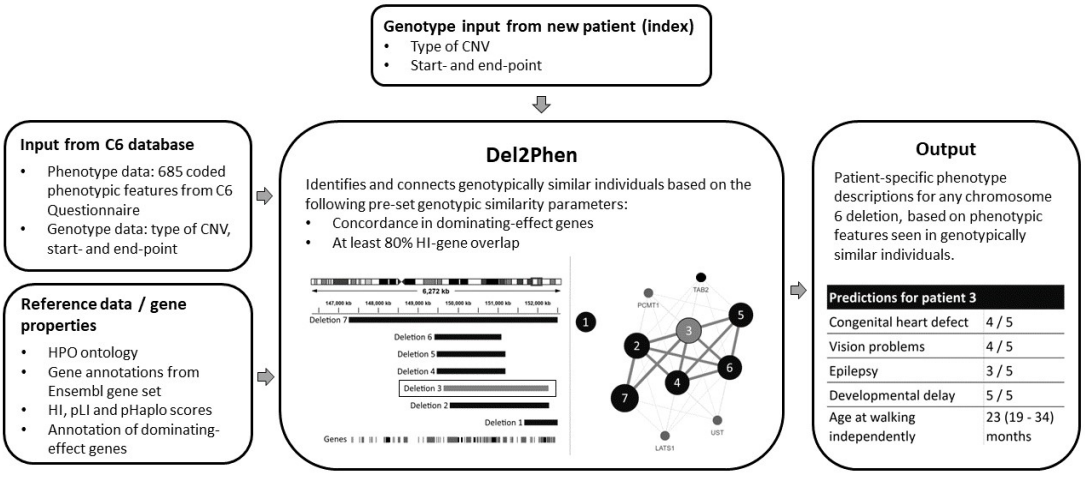

Figure 1. Schematic representation of Del2Phen. The tool uses the data collected through the C6P and stored in the Chromosome 6 database (input, left panel) to identify individuals with a similar deletion to that of a new patient with unknown phenotypes (middle panel). It then produces a phenotype description tailored to the deletion of the new patient (output, right panel). Deletions are deemed similar based on the following pre-set genotypic similarity parameters: (i) concordance in the involvement of genes with a highly penetrant and distinct phenotypic effect (dominating-effect genes), and (ii) at least 80% overlap in HI-gene content. Patients that are marked genotypically similar by the tool are grouped together, and their phenotypes are used to give a phenotype description for the new patient.

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ID 29

The association between autism and genetic syndromes

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Autism is characterized by difficulties with communication and social interaction, as well as repetitive and stereotypical behaviour. The cause of autism is largely genetic, but people with autism constitute a highly heterogeneous group (see figure). Diagnosing autism in addition to a genetic syndrome is useful because people with autism have specific educational needs. Structure and predictability, language and often communication support, and help with social interaction are considered core educational principles for individuals with autism.

An increasing number of genetic variants are being identified as being associated with autism. However, there is no evidence of 'autism-specific' genes. Rare genetic variants associated with autism are also associated with intellectual disability or other neurodevelopmental disorders. There is a long and complex developmental pathway from brain formation and synaptogenesis starting in the womb, to the symptoms that define autism, which often become apparent during the first two years of life.

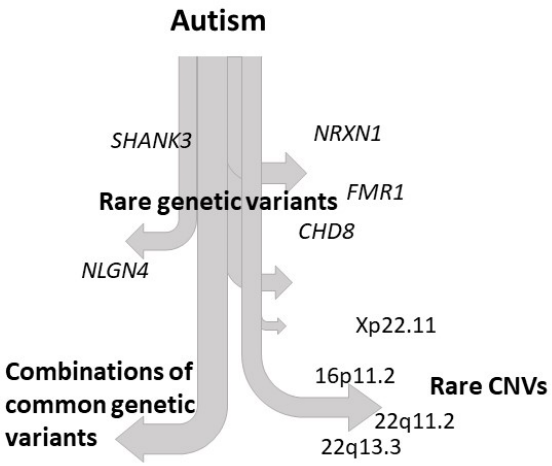

Figure: Among those with average or above average intelligence, the genetic risk for autism is typically due to the sum of effects of several common genetic variants, whereas in others the genetic cause of autism is explained by the effect of a single rare genetic variant.

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ID 30

Rare genetic syndromes with specific and ordinary clinical challenges; examplified by phelan mcdermid syndrome

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Background:
There are several rare genetic syndromes associated with neurodevelopmental disorders and many new genetic syndromes will probably be identified, both rare and ultra-rare. Development of clinical guidelines and specific services for each syndrome seems overwhelming and not feasible due to the large number of syndromes and the variation in behavioral phenotype within each syndrome.

Objectives:
To suggest a model for how to address the development of services and guidelines.

Method:
Recognition of common and specific areas of difficulties may be beneficial in the development of services and guidelines. By using Phelan McDermid syndrome as an example, a model for combining general and specific knowledge will be suggested.

Discussion:
Phelan McDermid syndrome is a rare genetic disorder representing a composed behavioral phenotype with varying medical, behavioral and psychiatric complications. The individuals will need thorough multidisciplinary assessments and monitoring. Identification of the level of difficulties within the different areas of difficulties usually represent ordinary clinical tasks which professionals in the Habilitation services (services addressing intellectual disabilities) often experience and are trained to perform.

However, Phelan McDermid syndrome are also associated with unique challenges, like for example loss of skills, and the combination of higher pain threshold, severe somatic illness and large communication problems, which may result in diagnostic overshadowing. That is when a disorder or a problem is considered as part of the genetic syndrome and therefore not identified. Treatable illness may be wrongly interpreted or not recognized. The challenge is to disentangle what is related to the specific genetic syndrome, what is related to autism or ID, and what is related to co-occurring psychiatric disorders.

Conclusion:
In order to develop services and guidelines there is necessary to avoid determinism, identify the specific challenges in each genetic syndrome, and combine these with ordinary interventions in the field of habilitation. In addition, the large variation in behavioral phenotypes indicate individual assessment and treatment plans.

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ID 31

Fragile X syndrome – should it still be considered as a first line test in children with developmental delay?

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INTRODUCTION: Fragile X syndrome (FXS) is considered to be one of the most common cause of intellectual disability in males. We have decided to analyze the incidence of FXS among our Genetic Clinic patients.

METHODS: During the last 8 years there were almost 40 000 patients' visits, of both children and adults, with homogenous genetic background (Polish), to the Outpatient Genetic Clinic, in the University Clinical Centre Hospital in Gdańsk, Poland. There were 3987 patients admitted due to ID/DD/autistic spectrum disorder based on ICD-10 diagnosis, which is about 10% of total number of patients. Every year the amount of patients admitted to the Genetic Clinic was higher, from 2879 in 2015 to 7306 in 2023, the same as the number of ID/DD/ASD patients, of whom the number was also increasing from 6% to 12% of total number of patients admitted.

We analyzed the number of performed tests in case of suspicion of FXS. The Genetic Laboratory has performed the molecular analysis of the region containing CGG repeats in the 5' UTR of the FMR1 gene using the AmplideX FMR1 PCR Kit (Asuragen, REF 76008, 49513). The test was based on the amplification of genomic DNA using the TRP PCR (Triple Repeat-Primed PCR) method and fragment length analysis using capillary electrophoresis.

RESULTS: There were 1028 genetic tests for FXS performed (from 0 in 2015 to 238 in 2023), with 12 results positive. Additionally, 3 results were inconclusive, of whom patients were finally diagnosed with Klinefelter syndrome, and there were 2 girls – with full mutations (siblings of affected boys) and 3 with premutation. Medical information about 12 FXS cases will be presented.

CONCLUSIONS: Above mentioned results of such a small number of FXS patients diagnosed, raise a question, if such test should still be performed as a first line analysis in ID/DD/autism group of patients. Further testing using aCGH/ES approach should be performed in the remaining patients, to better understand the complexity of DD/ID

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ID 33

From Craniofacial Development to Psychosis: Deciphering the Impact of a rare EFTUD2 Variant in a Case Early Onset Schizophrenia with Dysostosis Mandibulofaciale and Microcephaly. A Case Report.

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Background: Mandibulofacial Dysostosis Microcephaly syndrome (MFDM) is a rare genetic disorder associated with heterozygous mutations in the EFTUD2 (elongation factor Tu GTP binding domain containing 2) gene, primarily characterized by craniofacial anomalies and intellectual disabilities. However, limited studies have explored the psychiatric manifestations of this syndrome, including Early-Onset Schizophrenia (EOS).

Case Presentation: We report the first clinical case of a 36-year-old male with MFDM syndrome associated with an EFTUD2 mutation, presenting with EOS and rhombencephalosynapsis, a rare neurological condition. The patient exhibits facial dysmorphia, microcephaly, mild intellectual disability, motor disturbances, and a complex psychiatric history, including delusional episodes and hallucinations. Genetic investigations confirmed the EFTUD2 mutation, and imaging studies revealed rhombencephalosynapsis.

Discussion: This study highlights the exceptional association of early-onset schizophrenia and rhombencephalosynapsis with MFDM syndrome. EFTUD2 mutations, typically associated with craniofacial anomalies, demonstrate rare psychiatric manifestations, expanding the clinical understanding of this syndrome. The case also underscores the rarity of rhombencephalosynapsis in association with schizophrenia suggests a possible role of the EFTUD2 gene in psychiatric disorders.

While methodological challenges persist, including gaps in imaging data and the rarity of MFDM syndrome. The findings demonstrate the utility of a multidisciplinary approach to characterize these complex cases and suggest avenues for future research to elucidate underlying mechanisms.

Conclusion: This case highlights the significance of considering psychiatric aspects in the context of rare genetic disorders. A profound understanding of these associations can not only improve patient care but also contribute to expanding knowledge about the genetic mechanisms of psychiatric disorders. Future research is needed to further illuminate these connections and guide diagnostic and therapeutic approaches.

Keywords: Early Onset Schizophrenia; Case Report; EFTUD2; Mandibulofacial Dysostosis; Microcephaly.

ID 41

Identifying novel candidate genes and variants in a turkish cerebral palsy cohort: Utilizing whole and clinical exome sequencing data for improved diagnostics

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AIM Cerebral palsy (CP) is a non-progressive neurodevelopmental disorder affecting approximately 1 in 500 children globally, characterized by impaired motor functions and posture development. While the cause of CP remains elusive, various prenatal, and perinatal environmental risk factors such as prematurity, hypoxia-ischemia, and placental pathologies have been identified. Additionally, a considerable portion of CP cases lack identifiable environmental factors, suggesting potential associations with congenital brain abnormalities or genetic alterations.

Cohort-based exome sequencing is an effective method for identifying rare genetic variations that cause diseases. Given the phenotypic diversity associated with genetic disorders, sequencing technologies are invaluable for determining the genetic underpinnings of such conditions. The objective of our study is to enhance the rate of accurate diagnoses by reanalyzing the clinical and whole-exome sequencing data of unsolved patients with CP.

MATERIALS AND METHOD Fifty-nine unsolved cases with CP and CP-like symptoms were selected for reanalysis. DNA samples and related exome data were integrated into ACU Biobank (https://www.acibadem.edu.tr/biyobanka). The re-processing of raw data was conducted with an in-house developed genome analysis pipeline, GENNEXT (https://github.com/GenivaInformatics/gennext-workflows),

The workflow consists of an initial quality assessment of raw sequencing reads using FastQC, followed by data trimming with Trim Galore, sequence alignment to the human reference genome using SNAP, generating a SAM file, and Elprep utilization for post-alignment processes. GVCFs are produced in two different variant callers GATK haplotype caller and deep variant caller. Joint calling was done by GATK's GenotypeVCFs tool. Finally, VCF files were annotated with the GENNEXT annotation tool. Variant filtering and prioritization were based on minor allele frequencies and variant effects.

RESULTS and CONCLUSION The reanalysis identified that 37.9% (22 out of 58) patients harbored pathogenic or likely pathogenic variants in genes previously associated with CP, such as *SCN2A, WWOX, CTNNB1*, and *EMD*. In addition, variants of uncertain significance (VUS) were detected in 33.89% (20 out of 58) of cases within genes correlating to the observed phenotypes. Furthermore, 37.9% (22 out of 58) cases were found to have at least one risk factor linked to CP, including prematurity, placental pathology, and intrauterine growth restriction or infection. Notably, one individual was identified with two pathogenic variants in the *ASXL1* and *SETBP1* genes. These findings underscore the significant role that Mendelian variants play in CP etiology, alongside known environmental risk factors.

The study reveals significant genetic diversity within CP, indicated by the detection of deleterious variants in genes not previously associated with the disorder, pointing to extensive genetic heterogeneity. These initial findings emphasize the complex genetic landscape of CP, often reflected in its clinical variability. Research in this area will contribute to the elucidation of the genetic etiology of CP and differential diagnosis.

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Multidimensional impairment: Exploring the diagnostic concept through two case presentations with rare genetic variants

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Background: This work delves into the diagnostic concept of Multidimensionally Impaired (MDI) by discussing two clinical cases initially suggestive of mild intellectual disability. Both cases underwent genetic explorations, revealing rare genetic variants, the phenotypes of which are described, and their pathogenicity is discussed.

Case Presentation: The first case involves a 10-year-old patient initially diagnosed with mild intellectual disability. Genetic analysis identified a heterozygous microdeletion in 6q25, affecting the *ARID1B* gene. This gene is implicated in the SWI/SNF complex, involved in gene expression and chromatin organization. Contrary to the expected Coffin-Siris syndrome phenotype, this patient exhibited remarkable progress, evolving into a MDI diagnosis, encompassing developmental coordination disorder, neurovisual impairment, mild attentional issues with sluggish cognitive tempo, and learning difficulties. Notably, the patient is currently attending a regular school setting, demonstrating substantial improvement compared to initial developmental delays.

The second case involves a 11-year-old patient who first presented with hypotonia, regulatory difficulties, delayed language, and general developmental delays. Genetic testing identified a novel likely pathogenic variant in the TRAF7 gene inherited from the asymptomatic father (NM_032271.3(TRAF7):c.1853G>A p.(Ser618Asn)). The patient's multidimensional developmental issues now only include mild coordination disorder, dyslexia-dysorthographia, attention deficit hyperactivity disorder (ADHD), executive dysfunction, dysgraphia, and anxiety. Notably, the WISC assessment at age 7 revealed a heterogeneous profile, with particularly strong performance in areas such as comprehension (ICV at 100) and reasoning ability (IRF at 97), showcasing positive outcomes in specific cognitive domains despite the anticipated impact of the identified genetic variant.

Discussion: These cases underscore the importance of genetic assessments for patients with multidimensional developmental impairments, emphasizing the variable expressivity and incomplete penetrance often associated with these conditions. Understanding the concept of increased vulnerability and the interplay of genetic risk factors is crucial. The evolving nature of genetic discoveries emphasizes the need for repeated genetic evaluations throughout life.

Conclusion: The presented cases highlight the intricate nature of Multidys diagnoses, challenging conventional expectations associated with certain genetic variants. By emphasizing the evolving nature of genetic understanding, this presentation underscores the importance of ongoing genetic assessments for individuals with multidimensional developmental challenges.

Keywords: *Neurodevelopment; Case Report; ARID1B; TRAF7; Whole Genome Sequencing; Multidimensional Impairment.*

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Confirmation and expansion of the tceal1 related neurodevelopmental disorder fenotype

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Numerous contiguous gene deletion syndromes causing neurodevelopmental disorders have previously been defined using cytogenetics for which only in the current genomic era the disease-causing genes have become elucidated. One such example is deletion at Xq22.2, previously associated with a neurodevelopmental disorder which has more recently been found to be caused by *de novo* loss-of-function variants in *TCEAL1*. So far, a single study reported six unrelated individuals with this monogenetic disorder, presenting with syndromic features including developmental delay especially affecting expressive speech, intellectual disability, autistic-like behaviors, hypotonia, gait abnormalities and mild facial dysmorphism, in addition to ocular, gastrointestinal, and immunologic abnormalities. Here we report on four previously undescribed individuals, including two adults, with *de novo* truncating variants in *TCEAL1*, identified through trio exome or genome sequencing, further delineating the phenotype of the *TCEAL1*-related disorder. Whereas overall we identify similar features compared to the original report, we also highlight features in our adult individuals including hyperphagia, obesity, and endocrine abnormalities including hyperinsulinemia, hyperandrogenemia, and polycystic ovarian syndrome. X chromosome inactivation and RNA-seq studies further provide functional insights in the molecular mechanisms. Together this report expands the phenotypic and molecular spectrum of the *TCEAL1*-related disorder which will be useful for counseling of newly identified individuals and their families.

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Compound heterozygous variants in the non-coding RNU12 gene in two siblings with neurodevelopmental and movement disorder

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Splicing is a complex process that has not yet been fully understood. However, what we do know is that the splicing machinery involved in the processing of mRNA consists of two parts: The major and the minor spliceosome. One of the components of the minor spliceosome is the U12 small nuclear RNA (snRNA), which is encoded by the RNU12 gene, and that has only recently been linked to disease. Two distinct phenotypes have been associated with biallelic mutations in the RNU12 gene:

1. CDAGS syndrome which is characterized by Craniosynostosis and Clavicular hypoplasia, Delayed closure of fontanel, Anal anomalies, Genitourinary malformations, and Skin eruption and.
2. early-onset spinocerebellar ataxia type 33 with neurodevelopmental disorder features, for which to our knowledge only one family has been described in the literature (Elsaid et al. 2017).

Here, we report on two adult sisters from unaffected parents who presented with intellectual disability and a movement disorder. They were diagnosed with speech and motor delay in their early childhood, but no genetic testing has been performed so far. After excluding chromosomal aberrations, changes in gene doses (array-CGH), and Friedreich-Ataxia as a cause of their symptoms we performed whole exome sequencing and identified two compound heterozygous variants in the RNU12 gene in both sisters. Both variants are located at positions that are important for the stability of the U12 snRNA. Unstable U12 snRNAs are prone to degradation and hence can trigger a cascade of splicing-irregularities affecting many different genes.

Due to the limited number of patients with spinocerebellar ataxia type 33 described up to date and the lack of RNA analyses to further prove the pathogenicity of the two identified variants in the RNU12 gene the role of these variants regarding the phenotype of our patients remains to be determined. However, we strongly believe that these two variants contribute to the symptoms observed in our patients who fit the description of spinocerebellar ataxia type 33. This would be the second family with spinocerebellar ataxia type 33 reported worldwide caused by biallelic mutations in the RNU12 gene.

Most likely more patients with non-coding variants will be identified in the near future since whole genome sequencing is becoming a frequently used tool in routine diagnostics. This will not only help to better understand disease mechanisms of splicing but in the case of the RNU12 gene also help to delineate genotype-phenotype correlations.

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Reanalysis of whole exome data lead to diagnosis in unsolved patient with intellectual disability, spastic paraparesis, retinitis pigmentosa, hearing loss and dysmorphic facies

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Introduction: Re-analysis of exome sequencing data is one of the most important tools for identifying causative genetic variants. Here we present a patient with severe intellectual disability, spastic paraparesis and dysmorphic features who was diagnosed with MORC2-associated syndrome by Solve-RD reanalysis.

Patient: The index case, currently a 25-year-old male, was born at term after normal pregnancy and perinatal periods. Subsequently, he developed moderate intellectual disability, spastic paraparesis, retinitis pigmentosa and hearing loss. Other features include facial dysmorphism, short stature, microcephaly, and scoliosis. At the age of 14, he developed rectal adenocarcinoma.

Results: Examination of karyotype, chromosomal breaks and array-CGH and sequencing of genes ERCC6 and ERCC8 revealed no significant pathology. Clinical exome testing (Focused Exome, Agilent) was performed in 2018 with no finding of a pathogenic variant. Subsequently, whole exome sequencing in TRIO mode was performed at two sites in 2019. The MedExome library (Roche) and the HiSeq 2500 sequencer (Illumina) were used for these purposes in both cases. This investigation led to the discovery of a de novo variant c.229G>C p. (Asp77His) in the MORC2 gene. In 2019, the MORC2 gene was associated only with the development of Charcot-Marie-Tooth 2Z disease. As the patient's condition was not consistent with this disease, whole genome sequencing was indicated in October 2019. Analysis of WGS data did not lead to further findings of a pathogenic variant. WES data were uploaded to the GPAP platform. In 2022, a reanalysis of these data was conducted by the Solve-RD consortium, and our institution was notified of the inclusion of the MORC2 gene as an intellectual disability-associated gene. The phenotype of the patient fully correlated with the phenotype of the patients described in the 2020 publication.

Conclusion: The presented case proves the necessity of continuous exome data reanalysis, especially in unsolved cases which were examined using previous bioinformatics protocols.

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Pallister-killian syndrome: neonatal phenotype and key elements for timely diagnosis

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Background: Pallister-Killian syndrome (PKS – OMIM #601803) is a rare disease characterized by facial dymorphisms, congenital malformations of various organs and systems – particularly cardiac and gastrointestinal – hypo-hyperpigmentation streaks, epilepsy, cognitive disability and neurodevelopmental delay.[1] In the majority of cases, the disease is due to the presence of a supernumerary 12p isochromosome present in a tissue-limited mosaic pattern, with variable levels of mosaicism in different tissues with no evidence of genotype-phenotype correlation.[2] The aneuploidy is more easily detected in fibroblasts than blood, presumably due to loss of this isochromsome in hematopoetic lineages with age, or with in vitro culture of lymphocytes.[3] However, the diagnosis of PKS often requires clinical suspicion and, even with array-based diagnostics, often requires analysis of tissues other than blood to establish the diagnosis.[4] Therefore, it is necessary to outline, at an early stage, features that can assist the clinician in achieving early diagnostic framing in order to provide prompt multidisciplinary management of PKS. This retrospective study aimed to focus on the characteristics of pregnancy and the perinatal period to obtain a description of the neonatal PKS profile.

Method: Families (Italian and non-Italian) with whom the Italian Pallister Killian Association (a group of Italian families with PKS patients) has a collaborative relationship were contacted and, prior informed consent, all available clinical, laboratory and instrumental documentation relating to the neonatal and post-natal period was collected (38 patients). In addition, all the iconographic material (photographs, video recordings) voluntarily made available by the relatives of the patients examined (22 patients) was collected and viewed by the research team. At the same time, a literature review was conducted on PubMed up to October 2019, and all cases of neonatal PKS where time-referable data were available (75 cases) were recorded. Comparison of the study population with those in the literature was performed using Fisher's exact test. In the presence of at least one frequency value greater than 5, the $\chi 2$ test with Yates correction was applied. A statistical significance level of $p < 0.05$ was assumed.

Results: Comparison between our cohort and the cohort extracted from the literature reveals significant differences in gestational age at birth and anthropometric parameters, with prevalence in our cohort of newborns appropriate for gestational age in weight and length. Dysmorphic features present at birth in more than half of the population are: temporal stempling and sparse eyebrows, broad forehead, frontal protuberances, hypoplastic supraorbital arches, bitemporal narrowing, hypertelorism, often in association with telecanthus, broad nasal root and depressed nasal bridge, anteverted nostrils, elongated nasolabial philtrum, and thin upper lip with typical central incision. Significantly more frequent in our cohort is the presence of some congenital anomalies (sacral dimple 28.9% vs 9.3% of cases, anterior anus 31.6% vs 5.3% of cases, cardiac septal defects 36.8% vs 13.3% of cases), while the incidence of congenital diaphragmatic hernia is significantly lower (7.9% vs 22.7%). Only 15.8% of our patients have skin striae reported in the neonatal period. Neonatal hypotonia represents a fact reported in almost all the cohort analyzed (97.4%). No deaths occurred in the neonatal period ($p < 0.001$). 18.4% of the analyzed cohort received a diagnosis in the neonatal period. Spearman's correlation revealed a direct relationship between age at diagnosis and age at the time of the study, meaning that younger patients received an earlier diagnosis, probably because of better clinical recognition and thanks to new diagnostic techniques. Regarding postnatal diagnostic techniques, available data

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confirm greater diagnostic sensitivity in the study of skin fibroblasts rather than peripheral venous blood lymphocytes (93.8% vs. 36.2%) and in the use of FISH or micro-array techniques (CGH, SNP) rather than simple karyotype (73.5% vs. 51.9%).

Discussion:

Our study represents the largest analysis on neonatal data of a PKS cohort, providing an opportunity to accurately describe the characteristics of PKS in the neonatal period. Comparison with data from the literature (individual case reports focusing on different elements each time) reveals differences presumably due to ascertainment bias and information bias. Recurrent dysmorphological features combined with hypotonia data form the basis for a gestalt diagnosis by the clinician, which is necessary to perform the specific genetic investigation. By comprehensively analysing the abnormalities present in patients observed as early as the neonatal period and combining these findings with the data that emerged in the context of perinatal hospitalization, it is necessary to involve multiple professionals for appropriate multidisciplinary management when faced with a diagnosis of PKS or suspected PKS.

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Mapping the trajectory of syt1-associated neurodevelopmental disorder (baker-gordon syndrome)

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BACKGROUND. Synaptotagmin 1 (SYT1) is a presynaptic protein that mediates synaptic vesicle exocytosis and calcium-dependent neurotransmitter release. *De novo* variants in the *SYT1* gene manifest as *SYT1*-associated neurodevelopmental disorder (Baker-Gordon syndrome [BAGOS]), which is characterized by infantile hypotonia, moderate to profound global developmental delay, ophthalmic deficits, early-onset involuntary movement disorders, and EEG abnormalities in the absence of overt seizures. As more BAGOS cases have been diagnosed since the first reported case by our lab (Baker et al., 2015), the spectrum of clinical symptomology has expanded in breadth, diversity, and temporal heterogeneity (Baker et al, 2018; Melland et al, 2022). However, there is limited information concerning the developmental trajectory of diagnosed individuals.

OBJECTIVE. To produce the first developmental timeline of BAGOS, characterizing the broad spectrum of clinical symptomology and respecting both the (i) inter-individual gene variant-associated diversity and (ii) intra-individual temporal-based diversity.

METHODS. Clinical histories and standardised parent/guardian-report behavioural questionnaires were collated from 36 individuals diagnosed with BAGOS—recruited as part of the Brain and Behaviour in Neurodevelopmental Disorders of Genetic Origin (BINGO) project—enabling quantitative comparisons across the disorder. Specific measures included: (i) a study-specific Medical History Questionnaire; (ii) the Vineland Adaptive Behaviour Scales (third edition); (iii) the Developmental Behaviour Checklist 2 (DBC-P); (iv) the Activity Questionnaire (TAQ); (v) the Social Responsiveness Scale (SRS); (vi) the Repetitive Behaviour Questionnaire (RBQ); and (vii) the Cerebral Visual Impairment (CVI) assessment.

RESULTS AND CONCLUSIONS. The clinical and behavioural compendium was used to devise a comprehensive overview of our current knowledge of the developmental trajectory of BAGOS. This structured template characterizes the spectrum of clinical symptomology (cross-sectional analysis), how the phenotype changes over time (longitudinal analysis), and whether this is related to the specific *SYT1* gene variant identified. Our ongoing work seeks to: (i) expand this data repository by collecting at-home EEG measures of all individuals within the BINGO consortium; and (ii) partner with academic institutions and/or industry to better elucidate the effects of presynaptic dysfunction on developing neural cell populations, circuits, and systems, with the intention of identifying novel targets for treatment *[collaborators include Cambridge Stem Cell Institute, Florey Institute of Neuroscience, National Institute of Child Health and Human Development (NICHD)]*.

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Genome sequencing supports the role of *scn1a* and *pcdh19* in patients with undiagnosed dravet syndrome and related disorders

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Background: Dravet syndrome (DS, OMIM: 607208) is a rare developmental and epileptic encephalopathy of childhood. DS is clinically and genetically highly homogeneous. More than 85% of patients with DS have pathogenic variants in *SCN1A*. However, in negative cases of *SCN1A* mutations, mimickers have been implicated including most commonly *PCDH1*9. Although Gene panel, Exome Sequencing (ES) and associated techniques reveal most of the causative pathogenic variants, about 3 % of patients remain without molecular confirmation and fail to benefit from targeted therapies. Herein, we report findings from undiagnosed individuals meeting clinical criteria of DS who have been analyzed with Genome Sequencing (GS) through the national initiative "France Médecine Génomique 2025" (FMG-2025).

Methods: Our study involved previously unsolved cases of febrile seizure and drug-resistant epilepsy, broadly explored by array-CGH, gene panel of monogenetic epilepsy (PAGEM) and/or ES. Clinical presentation was assessed by physicians from reference centers.

Trio-GS was performed at the two FMG 2025 labs: SeqOIA and AURAGEN. An accurate bioinformatics workflow covered the detection and interpretation of single-nucleotide variants (SNVs), small insertions and deletions (INDELs), uniparental disomy, copy number variants (CNVs), balanced structural variants and short tandem repeat expansions. Analysis was carried out focusing on medically relevant variants. Validation was carried out by a group of experts.

Results: Our study included 320 patients with epilepsy. Overall, 12 individuals (3.8%) presented febrile seizure and drug-resistant epilepsy in alignment with DS and related disorders.

For these 12 patients, 8 medically relevant variants were identified (67%) in mainly two causative genes: *SCN1A* (n=6) and *PCDH19* (n=2). All variants occurred *de novo.*

Four deep intronic SNVs were identified in *SCN1A* and were predicted either to induce a poison exon or to alter the splicing process. Two deletions affected a part of *SCN1A* exon 21 and *PCDH19* exon 1 and were missed by the exome CNV pipeline. A deletion of 5'UTR exons of *SCN1A,* not captured through panel sequencing, was also identified. Finally, a heterozygous complex rearrangement of *PCDH19* was incompletely resolved through short-read sequencing. It was a double intragenic duplication affecting exons 4 and 5 with an inverted fragment.

Discussion : We report the first results of GS among genetically undiagnosed patients with a strong clinical semiology of DS and related disorders. The number of patients is relatively limited in the context of the FMG-2025 due to the high molecular diagnostic yield in DS with ES and PAGEM. Nevertheless, GS showed variants of interest in *SCN1A* and *PCDH19* missed with the previous methods of investigation confirming genetic homogeneity. Functional studies based on RNA sequencing and minigene tools are currently been completed to evaluate the variants' impacts on the proteins.

Early diagnosis is crucial in DS to direct antiepileptic drug selection away from agent-exacerbating seizures and to prescribe targeted therapies such a stiripentol. An early control of seizures may dramatically improve patients 'cognitive and behavioral functioning.

Keywords:

Genome Sequencing, epilepsy, epilepsy with febrile seizures, Dravet syndrome

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ID 81

Clinical and molecular characterization of a patient presenting with neurodevelopmental disorder and multiple congenital abnormalities, carrying homozygous pathogenic variant in GZF1.

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Within the intricate landscape of neurodevelopmental delays, the gene *GZF1* has emerged as a compelling candidate in neurodevelopmental disorders.

We report a child who was referred to our genetic unit in Lyon. He was born to first-degree cousin parents within a family of four children, the other siblings were healthy without notable issues. However, our patient faced challenges from birth. He was born at 39 weeks of pregnancy characterized by intrauterine growth restriction; his birth weight was 2800g (-1.7SD); length was 43 cm (-3.7 SD); occipital-frontal circumference (OFC) was 36cm (+0.9SD). Micrognathia was observed with initial feeding difficulties requiring nasogastric feeding tube. He experienced neonatal seizures, which were controlled by valproic acid, subsequently stopped. Brain MRI and EEG were normal. Developmental delay was observed: he started walking at 18 months and pronouncing first words at 30 months; he also had learning difficulties and attended a school for children with special needs.

He presented several medical problems. First Ponseti method and then surgical correction were performed for bilateral clubfeet. Hip dysplasia was discovered, prompting the use of a cuddly diaper. Due to prenatal onset short stature, growth hormone therapy was performed from the age of 3 to 10 years, leading to no significant effect. Other comorbidities included severe scoliosis requiring corset, bilateral hearing loss, unilateral myopia with amblyopia, and dental abnormalities (amelogenesis imperfecta; abnormally shaped and misaligned teeth) and high arched palate required maxillary distractor. Echocardiography showed superior vena cava opening into the coronary sinus. At the age of 12 years and 3 months, his OFC was 52.5 cm (-1SD), height 126.5 (-3SD), weight 24.2Kg (-3 SD), BMI 15.2 (5^{th}). Distinct physical features were noted including epicanthus; hypertelorism; eyelids ptosis; arched eyebrows; small, low-set and posteriorly rotated ears; thin upper lip; retrognathism; short and wide neck with pterygium colli; and camptodactyly.

Genetic assessment, including standatd karyotype, Chromosomal Microarray, and gene panel for RASopathies, was normal. Whole Genome Sequencing (WGS) *in trio* performed in AURAGEN laboratory (*Plan France Médecine Génomique 2025*) showed homozygous premature stop variant pGln131* in the *GZF1* gene inherited from both parents, and classified as pathogenic according to ACMG guidelines.

This result was discussed in a multidisciplinary clinical-biological meeting in our genetic unit. Bi-allelic pathogenic *GZF1* variants have been previously reported in individuals showing a Larsen-like syndromic picture named “joint laxity, short stature, and myopia” (OMIM #617662) featuring peculiar morphological traits, eye problems (severe myopia, retinal detachment, glaucoma, ocular colobomas), progressive hearing loss, clubfeet, kyphoscoliosis, congenital heart defects, and joint hyperextensibility with multiple dislocations. In our patient, despite the absence of joint hyperlaxity (Beighton score was assessed as 0), the *GZF1* defect is considered to be pathogenic, explaining the observed phenotype (short stature, phenotypic variants, scoliosis, myopia, deafness, clubfeet).

Since our study suggests that Larsen-like joint laxity is not a constant feature of *GZF1* related syndromic picture, the question about the pertinence of the patronymic names used in the medical literature (‘Larsen syndrome’; “joint laxity, short stature, and myopia”) arises. The proband shows speech delay and learning difficulties associated with multiple

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congenital abnormalities: even if we cannot formally rule out the possibility that the observed neurological involvement is not related to *GZF1*, genome sequencing did not find any pathogenic variant in genes affecting neurodevelopment. Interestingly, there are few evidence in the literature showing that *GZF1* is involved in neurogenesis and neuronal migration. Further studies are needed to clarify the role of *GZF1* in neurodevelopment and to confirm that neurological involvement is part of the phenotypic spectrum of this condition.

In conclusion, we report a patient presenting with neurodevelopmental disorder and multiple congenital abnormalities carrying homozygous pathogenic variant in *GZF1*, providing new insights into the phenotypic spectrum of this ultra-rare condition.

ID 85

Coffin-Lowry Syndrome : Phenotypic spectrum in affected females

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INTRODUCTION

The Coffin-Lowry Syndrome (CLS) is a rare condition associated with the loss of function of the *RPS6KA3* gene (OMIM 300075), located on the X chromosome. Diagnosis is frequently clinically considered in boys, presenting with hypotonia, developmental delay, intellectual disability (ID), small stature, and distinctive craniofacial features. However, in females, the spectrum of symptoms differs, leading to delayed diagnoses, usually following identification in a male family member. This lack of understanding regarding the female phenotype hampers tailored management, neurological and orthopedic care, and impedes genetic counseling for affected families.

PATIENTS AND METHODS

This study reports the clinical, morphological, and neurodevelopmental phenotype of 19 females from 15 different families, diagnosed molecularly with CLS, who sought consultation at the Clinical Genetics Department of La Pitié-Salpêtrière Hospital between March 2016 and September 2023 (n=9), as well as patients recruited via collaboration calls (ERN-ITHACA, DéfiScience, AnDDI-Rares, n=10).

RESULTS

The majority of the patients experienced learning difficulties and benefited from specialized schooling (92%). Among evaluated patients (n=6), neurodevelopmental disorders (NDD) were observed, including mild (n=4) or moderate (n=1) ID, and complex NDD (n=1). Eight patients required psychiatric follow-up due to anxiety (n=6), a psychotic episode (n=1), or a clinical diagnosis of burn-out syndrome (n=1). Scoliosis was prevalent in 46% of evaluated patients. Typical facial and extremity characteristics of CLS were noted in 92% of cases. None of the patients experienced drop attacks or had a history of epilepsy.

DISCUSSION AND CONCLUSION

Limited patient series have focused on CLS in females. Existing literature reports inconsistent ID, learning difficulties, and rare psychiatric disorders. This study represents the most extensive phenotypic series in females with CLS to date. Our findings highlight that CLS in females presents as a distinct clinical entity, with a prevalent neurodevelopmental phenotype, predominantly characterized by ID and psychiatric symptoms.

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PERSPECTIVES

This study underscores the necessity for continuous follow-up and holistic care for diagnosed females with CLS, beyond mere genetic counseling. The study is ongoing, and we anticipate clinical data from at least additional 15 patients; our aim is to present comprehensive results encompassing all recruited patients.

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ID 86

Molecular diagnosis of Tay-Sachs disease: A Moroccan case report

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Introduction Tay-Sachs is a rare autosomal recessive neurodegenerative disease, fatal in its infantile form. It involves the accumulation of lipids, primarily in the nervous system, leading to severe neurological manifestations.

Objectives and Methods We present the case of a 12-month-old boy, born from a consanguineous marriage, admitted for diagnostic evaluation of psychomotor regression, generalized hypotonia, and seizures. In the patient's family history, a deceased brother under similar circumstances. The child was referred to us for genetic consultation and molecular study.

Results Ophthalmological examination revealed bilateral papillary pallor with a macular cherry-red spot. Hexosaminidase A enzyme activity was low. Brain MRI showed cerebral leukodystrophy. Exome sequencing indicated a homozygous mutation in the HEXA gene: NM_000520.6 :c.946del ;p.(Tyr316llefsTer24)

Discussion This condition is associated with a genetic mutation on chromosome 15, resulting in decreased enzymatic activity of hexosaminidase A. The inability to catabolize gangliosides leads to their accumulation in lysosomes, ultimately causing cell death. Gangliosides are ubiquitous lipids in the central nervous system, and any disruption in their metabolism or catabolism results in impaired nerve conduction.

Conclusion Currently, Tay-Sachs disease has no treatment, emphasizing the importance of genetic counseling and the potential for pre-implantation diagnosis.

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ID 88

Beaulieu-Boycott-Innes Syndrome as a rare genetic neurodevelopmental disorder caused by a novel homozygous variant in THOC6 gene in a sibling

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Background:

Beaulieu-Boycott-Innes syndrome (BBIS) is a new neurodevelopmental disorder characterized with global developmental delay, intellectual disability, microcephaly, dysmorphic feautures, structural cardiac and genitor-urinary anomalies and dental caries. To date, only 20 cases of BBIS have been reported in the literature, caused by biallelic variants in *THOC6* gene. We report here two new patients with a novel homozygous variant in this gene.

Patients and methods:

We report the case of two sibs referred for psychomotor delay and growth restriction. A standard karyotype was performed in a first-tier. In a second step, molecular investigation for Silver-Russel syndrome was carried on by Methylation-Specific Multiplex Ligation-dependent Probe Amplification (MS-MLPA) for both imprinting regions ICR1 and ICR2 on 11p15 locus, and for the MEST and the GRB10 loci on chromosome 7. Finally, whole-Exome-Sequencing (WES) was performed in the elder proband. Sanger sequencing was used for variant confirmation and family segregation study.

Results:

The sibs were a 4-year-old boy and a 9-months old girl, born from unrelated parents but originated from the same region. Low birth weight, neonatal hypotonia, chronic diarrhea and psychomotor delay were reported in both children. Feeding difficulties were also present in the girl with the need to nutripump.

On physical examination, they presented with microcephaly at -7DS and -5 DS respectively, low weight at -5 DS and -4 DS respectively. The boy had short stature at -4 DS. The same dysmorphic features were noticed in the two cases, including tall forehead, high anterior hairline, deep-set eyes, long nose with low-hanging columella, and protruding ears. Clinodactyly of the fifth finger, overlappig toes, and pectus excavatum were also shared skeletal anomalies in both sibs. Additional malformations were found, comprising auricular and ventricular septal defects and hypoplasia of the corpus collosum in the girl. Neither cardiac nor cerebral malformation was found in the boy, who had however bilateral cryptorchidism, sigmoid kidney and excretory system duplication. Standard karyotype was normal in both children, as well as the MS-MLPA study for chromosomes 11 and 7. WES revealed the homozygous c.859G>T variant (p.Gly287Trp) in the *THOC6* gene (NM_024339.5) classified as a variant of uncertain signification according to ACMG criteria. Family segregation found the same variant at the homozygous state in the affected sister and at the heterozygous state in both parents. The clinical presentation in our patients very suggestive of BBIS syndrome, as well as the family segregation, allowed us to upgrade the classification of the variant to likely pathogenic.

Conclusion:

This is a report of an additional case with very suggestive phenotypic presentation of BBIS syndrome confirmed at the molecular level with a novel variant enriching the mutational spectrum of *THOC6*.

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ID 89

Microcephaly, Epilepsy, and Diabetes Syndrome 1: A Moroccan case report of compound Heterozygous IER3IP1 mutations

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Microcephaly, Epilepsy, and Diabetes Syndrome 1 (MEDS1) is a very rare autosomal recessive neurodevelopmental disorder (OMIM#614231) characterized by the triad microcephaly with simplified gyration, neonatal permanent Diabetes and infantile epileptic encephalopathy. It is caused by biallelic mutations in Immediate Early Response 3 Interacting Protein 1 gene (*IER3IP1*), with only eleven reported cases to date. Here, we present an additional case of MEDS who is compound heterozygote with two different mutations in *IER3IP1*.

The proband, first-born child of a healthy non-consanguineous couple in northern Morocco experienced perinatal asphyxia at birth. Although his weight and length were within normal ranges, his head circumference was markedly reduced (−4 SD). At one month, the patient exhibited epileptic seizures, necessitating multiple hospitalizations. The electroencephalogram shows left temporal seizures, marked by disorganized background activity influenced by simultaneous partial epileptic discharges. Brain MRI revealed a diffuse simplified gyral pattern, predominantly frontal and occipital bilaterally, associated with agenesis of the corpus callosum. Two months later, the patient developed insulin-requiring permanent neonatal diabetes (HbA1c level of 12).

Clinical examination revealed hypotonia, severe developmental delay and dysmorphic features, including short forehead with bitemporal grooving, bulbous nose, big-ruddy cheeks, deep philtrum, small mouth with tented vermilion of upper lip, micrognathia, prominent ears and a short neck. Recurrent pneumonia infections complicated the clinical course leading to the patient's death at 1 year and 3 months. Whole exome sequencing analysis identified the patient as compound heterozygous for two *IER3IP1* variants:

NM_016097.5:c.62T>G p.(Val21Gly)

NM_016097.5:c.236T>G p.(Leu79Ter)

Segregation analysis revealed that the mother was heterozygous for the first variant, and the father for the second one.

The IER3IP missense variant p.Val21Gly , classified as pathogenic, has been previously reported in three other MEDS cases of different geographic origins. The nonsense variant p.Leu79Ter was not identified in any literature reports or the healthy population database (genomeAD). However, in silico prediction databases stated the variation as "deleterious.". According to The American College of Medical Genetics (ACMG) 2020 criteria, the variant is classified as pathogenic. The *IER3IP1* gene encodes a highly conserved protein localized to the endoplasmic reticulum (ER) potentially involved in the ER stress response by mediating cell differentiation and apoptosis. Loss of function mutations in the IER3IP1 protein leads to an imbalance between apoptosis and cell proliferation in pancreatic beta cells and the cerebral cortex which contributes to the development of diabetes and microcephaly. Further studies are crucial to better understand MEDS's pathophysiology.

Our patient exhibits a clinical presentation akin to previously documented cases of MEDS. This underscores the importance of considering MEDS in cases of permanent neonatal diabetes, especially when accompanied by significant head growth failure in a newborn infant. Recognizing this neonatal phenotype can enhance early diagnosis, prompt treatment, and accurate familial genetic counseling.

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ID 91

Interest of High-Throughput Sequencing in adult patients with intellectual disability.

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Intellectual disability (ID) is a common condition affecting around 2% of the general population. Expression and etiologies are highly variable and heterogeneous. The “intellectual disabilities of rare causes” referral center established in November 2005 a multidisciplinary consultation dedicated to adults with intellectual disability. The objectives of these consultations are multiple including etiological diagnosis, genetic counseling, treatment, phenotypic characterization of patients and evolution of these rare conditions.

Managing cases without an established etiological diagnosis presents more uncertainty. This uncertainty affected patients, due to a lack of data on progression, and their relatives, because of the absence of reliable genetic counseling.

The advent of advanced sequencing techniques has significantly increased the diagnostic yield in intellectual disability with a direct impact on genetic counseling. Our study involved adult patients, aged over 15 years and 3 months presenting intellectual disability, without an established etiological diagnosis. They are referred from different services: pediatrics (neuropediatric or pediatric genetics), adult units (neurology, nutrition, physical medicine and psychiatry), by their attending physician, a social establishment or at request of families or patient associations.

These patients underwent trio sequencing, either by Trusight one (TS1) from 2014 to 2016 or by Exome sequencing from 2016 to 2020 or by genome sequencing from 2021.

A pathogenic or probably pathogenic variant was identified in 50 % of patients. These diagnoses involved rare recurrent genes, a majority of de novo variants, some candidate genes currently undergoing validation, variants of unknown significance and variants explaining only part of the phenotype.

These findings underscore the critical importance of genetic diagnosis in intellectual disability even among adult patients. The genetic diagnosis has direct implications for genetic counseling, offers benefits for parents after years of diagnostic uncertainty, and provides valuable insights into the natural progression of these rare diseases in adulthood.

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ID 92

Psychomotor regression and mouvement disorder retalted to sucla2: A Moroccan case report

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Mitochondrial DNA (mtDNA) maintenance defect syndromes are a group of disorders characterized by defects in a number of nuclear gene-encoded proteins that are essential for nucleotide recycling, mtDNA replication, nucleotide transport from the cytosol, and mitochondrial fusion. Pathogenic variants in these genes result in impaired mtDNA synthesis, leading to quantitative (mtDNA depletion) and qualitative (multiple mtDNA deletions) defects in mtDNA. These defects result in insufficient synthesis of mtDNA-encoded proteins, manifesting as organ dysfunction in highly energy-demanding tissues due to inadequate ATP production, with a broad phenotypic spectrum.

We describe here the first evidence of SUCLA2-related encephalomyopathy in Morocco in a 19-month-old female child born to first-degree cousins. The child harbors a very rare homozygous variant classified as probably pathogenic (class 4) according to the American College of Medical Genetics and Genomics classification: SUCLA2(NM_003850.3): c. 1219C>T (p.Arg407Trp), identified by exome sequencing. The phenotypic manifestations of our patient include psychomotor regression after the 16th month of life, feeding problems, hypotonia, and movement disorder (athetosis). Cerebral MRI showed signal abnormalities in the putamen nuclei and globus pallidus. Biochemical screening showed an increased value of lactate in urine and cerebrospinal fluid (CSF) and a normal methylmalonic acid value in urine.

Our case expands the ethnic presentation and expression variability of SUCLA2-related encephalopathy associated with the p.Arg407Trp variant, known to cause a relatively mild presentation.

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ID 97

Grange syndrome, characterized by early-onset hypertension: preliminary finding of intellectual disability due to compound heterozygous YY1AP1 gene frameshift variants

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Grange syndrome (GRNG) is a rare disease with autosomal recessive inheritance that begins at an early age. It is characterized by hypertension and multifocal stenosis, or occlusion lesions of the renal, cerebral and abdominal arteries, accompanied by learning disabilities, bone fragility, syndactyly, brachydactyly and congenital heart defects. We report on the case of a 17-year old female with compound heterozygous framehisft pathogenic variants in YYA1P1 (c.1903_1906del, p.Glu636ProfsTer13 and novel (c.2051_2052del, p.Pro684ArgfsTer26) detected by clinical exome sequencing. This report was important in terms of diagnosis as a result of genetic tests performed for cognitive impairment, which is less reported in this disease, after admission to the child and adolescent mental health clinic, and screening for other serious findings in terms of morbidity and mortality.

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ID 98

Cohen syndrome: Can early-onset neutropenia and hypotonia provide early diagnosis and intervention for intellectual disability?

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Although Cohen syndrome is a syndrome associated with neurodevelopmental disorders, especially intellectual disability, neutropenia and recurrent infections are consistently reported in cases. Therefore, neutropenia is an important part of the syndrome as well as intellectual disability. Homozygous variants in the *VPS13B* gene, which is located on chromosome 8q22 and contains 62 exons, have been found to cause Cohen syndrome. The variability of the clinical findings and the appearance of some findings by older age may lead to a delay in diagnosis. We would like to emphasize the importance of early neutrophil count and hypotonia for early diagnosis and treatment options. Being able to diagnose Cohen syndrome before symptoms of intellectual disability occur may enable the early use of future gene therapies. The characteristics of 3 cases diagnosed with Cohen Syndrome, who were diagnosed at the Department of Medical Genetics at Balıkesir University and followed up for neuropsychiatric symptoms at the Department of Child and Adolescent Psychiatry, are summarized in Table 1.

	Case 1	Case 2	Case 3
Gender	Male	Female	Female
Age	7 years	6 years	15 years
Mutation Type	Missense	Frameshift	Nonsense
Protein Variant	p.Ser2748Leu	p.Leu3805ThrfsTer13	p.Gln327Ter
Mutation	Homozygous VPS13B(NM_152564.5):c.8243C> T	Homozygous VPS13B (NM_152564.5):c.11411dup	Homozygous VPS13B(NM_152564.5):c.979C>T
Birth	39 weeks	39 weeks	40 weeks
Birth Weight (Gram)	2580	2750	2500
Current Weight	23	16.5	63.4
Current Height	117	105	146.7
Walking Age (Month)	18	27 (accompanied by physiotherapy)	4 years old
First Words	5 years old	12 months	4 years old
Current Language Ability	Several words	Several words	sentences including two or three words

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Behavioral Anomalies	hyperactivity	hyperactivity	hyperactivity
Epilepsy	-	-	-
Additional Neurological Findings	-	-	-
Brain Imaging (MRI)	Normal	Normal	Normal
Eye Anomalies	It was normal at the check-up 3 years ago.	astigmatism she uses glasses.	Myopy She uses glasses. Macula hyperpigmentation, Optic disc problems
Other Clinical Findings	Feeding problems due to swallowing problems Feeding without chewing for the first 3 years	Feeding problems due to swallowing problems PFAPA milk allergy	Feeding problems due to swallowing problems Ongoing chewing problem sleep problems
Microcephaly	+	+	+
Intellectual Disability	+	+	+
Hypotonia	+	+	+
Hypermobile Joints	+	+	+
Neutropenia	+	+	+
Recurrent Infections	respiratory tract infections	respiratory tract infections	respiratory tract infections
Oral Aft	-	+	+ (chronic)
Trunchal Obesity	-	-	+
Psychiatric Family History	None	None	None
Other Medical Diseases in the Family	Father died due to malignant arrhythmia	Her father had asthma	thalassemia trait - carrier
Maternal Age at Birth	25	30	24
Father's Age at Birth	32	37	24
Siblings	9 year old, older sister (Healthy)	Her mother has an older brother from her previous marriage. (Healthy)	She has no siblings

		She has an older sister from his father's other marriage. (Healthy)	
Consanguinity	+	+	+
Special Education	since 2 years old	since 3 years old	since 4 years old

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- *abstracts* -

ID 23

Validation of a preclinical model for the evaluation and development of new therapeutic approaches in duplication 15q disease

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Dup15q syndrome is a neurodevelopmental disorder determined by the presence of one or more supernumerary copies of the q11.2-q13.1 region of chromosome 15 of maternal origin. Typical manifestations of the syndrome include central hypotonia, global psychomotor developmental delay, moderate to severe intellectual disability, autism, and epilepsy. Epilepsy affects more than 50 percent of affected individuals, most frequently begins in childhood, and is generally drug resistant. The frequency and severity of dup15q-associated epilepsy denote the need to deepen our knowledge of the mechanisms of epileptogenesis related to the syndrome and develop specific therapeutic strategies.

Fibroblast cell lines from four different patients were reprogrammed into induced pluripotent stem cells (hiPSCs) by the Austria-based company, Neurolentech GmbH. These cells will be differentiated into excitatory cortical neurons by overexpressing the neuronal determinant Neurogenin 2 (NGN2) upon doxycycline treatment, and then will be studied on micro-electrode arrays (MEAs), that allow non-invasive measurement of neuronal network activity.

We expect that the networks created by dup15q patients' neurons will show different types of activity compared to healthy subjects, leading to the identification of a signature, or "electrical signature", characteristic of the patients. Moreover, these neurons will be treated with possible drugs that could counteract epilepsy to evaluate the possibility of reversing this "electrical signature," returning it to the physiological levels observed in unaffected controls.

This study will allow the creation of an in vitro model and the identification of an electrical activity profile characteristic of dup15q patient-derived neurons. Moreover, this model could allow the in vitro testing of the efficacy of possible new drugs directly on patient-derived cells, enabling the development of personalized therapies.

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ID 32

Neuronal phenotypes associated with FBXO11-deficiency can be alleviated with chemical activation of the proteasome

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Haploinsufficiency of FBXO11 is associated with a variable neurodevelopmental disorder. So far, neither the underlying pathomechanisms nor the function of FBXO11 in the nervous system are well understood. Using a combined approach, we induced *FBXO11*-deficiency in a human stem cell based neuronal model and a *Drosophila* model. We performed transcriptomic analyses on neuronal material as well as molecular phenotyping in both models.

We found that loss of FBXO11 is associated with a range of neuronal phenotypes, including defects in neuronal migration, dendritic arborization and abnormal proliferation/differentiation balance. We could furthermore identify the stemness factor NANOG as a potential substrate of FBXO11 and therefore suggest a molecular link between disturbed neuronal function and proteasomal dysfunction in *FBXO11*-deficiency. Activating the proteasome with small molecules PD169316 and R-Verapamil could partially alleviate *FBXO11*-deficiency-associated phenotypes in the fly model. Our study shows the importance of FBXO11 for neurodevelopment and highlights the reversibility of related phenotypes, which opens an avenue for potential development of therapeutic approaches.

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ID 40

Integrating biological and neuropsychiatric underpinnings of neurodevelopmental disorders in order to design novel treatment strategies

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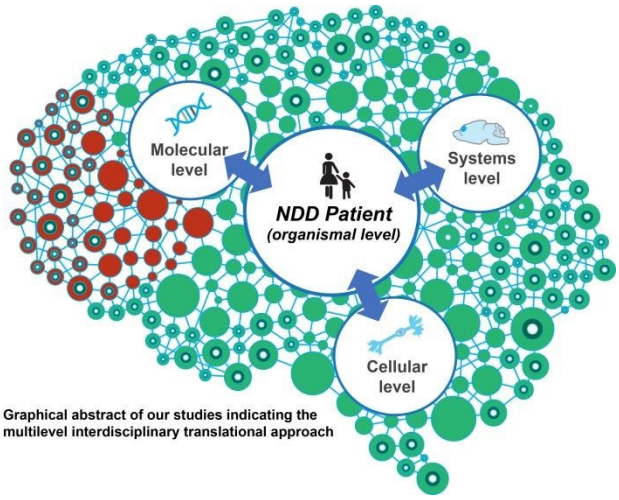
Neurodevelopmental disorders (NDDs) comprise a heterogeneous group of disorders with a large social impact. Frequently, similar genes appear affected by rare variants across NDDs and psychiatric conditions. The steep increase in gene discovery in these so-called Mendelian syndromes, syndromes caused by rare monogenic variants, allows us to study underlying neurodevelopmental biology and detailed clinical phenotyping. The implementation of tailored intervention(s) for rare ND syndromes 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*).



Graphical abstract of our studies indicating the multilevel interdisciplinary translational approach

Our multidisciplinary Radboudumc expert center for rare genetic NDDs is working hand-in-hand with various research groups on campus and in the Netherlands as well as with various industrial and societal stakeholders to continue studies from syndrome discovery to development of etiology-based strategies for personalised management/therapy. One example of such an interdisciplinary consortium is the NWA project *ProMiSe* in which we aim to understand the underlying neurocognitive and biological mechanisms of a set of NDDs (eg WitKoS, KBG). 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 novel intervention strategies for Mendelian disorders by obtaining fundamental insights in both the clinical and biological consequences of mutated genes that cause Mendelian syndromes. 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 possibilities for drug targeting. 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.

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ID 44

Mitotic defects in human ASPM microcephaly

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Primary Microcephaly is a disorder of brain growth responsible for motor and intellectual handicap. Primary microcephaly is caused by mutations in more than one hundred genes encoding proteins playing a role in centrosome duplication/cohesion, spindle pole positioning, mitotic division, DNA replication/repair.

Among these genes, ASPM (Abnormal SPindle-like Microcephaly) is the most frequently mutated. Asp in *Drosophila* localizes to microtubule minus-ends, and is known to play a crucial role in spindle pole focusing (Wakefield et al., 2001). *Asp* mutant neuroepithelium morphogenesis is impaired due to high levels of apoptosis of neuroepithelial cells after mitotic defects (Rujano et al., 2013). In mouse or ferret mutants, cortical surface or thickness are reduced owing to premature exhaustion of the neural progenitor pool explained by a switch from symmetric to asymmetric divisions of neural progenitors (Pulvers et al., 2010, Capecci et al., 2015, Johnson et al., 2018).

Importantly, little is known about the cellular and molecular consequences of *ASPM* mutations in the human progenitors. To answer to this question, we have characterized human ASPM fetal brains. We have found multipolar spindles in the apical progenitors of the ventricular zone. Further, using early organoids (neural rosettes) differentiated from hiPSCs reprogrammed from fibroblasts of patients carrying *ASPM* mutations, we showed disorganization of neural rosettes, and high levels of apoptosis. Interestingly, defects in spindle pole focus associated with PCM fragmentation, and centrosome amplification, which lead to the generation of multipolar spindles were also frequently noticed. This study identifies for the first time mitotic failure, resulting from multipolarity and consequent cell death or premature differentiation as a cause for human primary microcephaly.

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ID 49

Patients with Kabuki Syndrome type-1 and Kleefstra Syndromes Present Altered Immune Cell Responses

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Chromatinopaties are a group of rare congenital diseases caused by mutations affecting chromatin regulators involved in histone modifications and gene transcription. Kleefstra syndrome type 1 and type 2 result from mutations in *Ehmt1* and *Kmt2c* genes, respectively, while mutations in *Kmt2d* cause Kabuki syndrome type 2. Kmt2c and Kmt2d are primary histone 3 lysine 4 (H3K4) mono- and di-methyltransferases that activate the expression of target genes. Whereas Ehmt1 enzyme mono- and di-methylates H3K9 and causes transcriptional repression. Although patients present with various immunopathologies, among other disorders, the role of these enzymes in shaping immune responses is largely unknown. Furthermore, the plasticity of many immune cells, including monocytes and macrophages, regarding their functional responses are enabled by epigenetic mechanisms such as histone methylation.

To address the role of KMT2C and KMT2D methyltransferases in immune cells, we have examined the peripheral blood mononuclear cells (PBMCs) responses upon pro-inflammatory stimulation in patients with Kleefstra syndrome type-2 and Kabuki syndrome type-1. We observed that the haploinsufficiency of KMT2C and KMT2D attenuated IL-1ß and IL-18 expression upon LPS and *S. typhimurium* stimulation by PBMCs from these patients. Moreover, we observed the decrease number of specific immune cell populations such as CD4, Vd2, and NK T cells in peripheral blood of Kabuki patients.

Further, to study the role of EHMT1 in immune cells, we analyzed Kleefstra syndrome type-1 patients. EHMT1-haploinsufficiency results in elevated production of IL1ß and IL18 by PBMCs and monocytes upon stimulation with various stimulation agents compared to healthy controls. This effect could be reduced by an NLRP3-inflammasome-specific inhibitor, suggesting a role for EHMT1 in NLRP3 inflammasome activation. The production of other cytokines, such as TNF-a, IL6, IL8, and MCP1, remains unaffected between the two groups. Additionally, classical monocytes, CD4 and CD8 T cells in the periphery are significantly reduced in patients.

In the following steps, we aim to unravel the molecular mechanism by which EHMT1, KMT2C, and KMT2D regulate immune responses and whether disruption of this regulation contributes to the dysfunction of the immune system in the patients. This knowledge will be of particular interest for developing therapeutic strategies for tuning the production of proinflammatory cytokines and for managing immunodeficiencies exhibited by these patients.

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ID 55

Identification of a Cryptic Splicing Site in MED13L Intron 7 Leading to Truncated Protein in Patients with MED13L Syndrome

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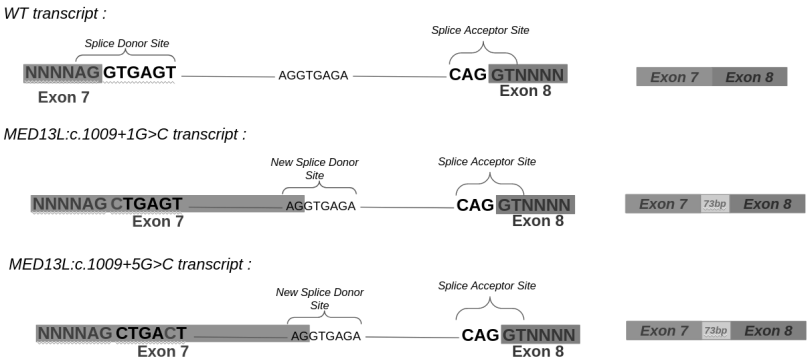

Background: *MED13L*, encoding a Mediator complex subunit, is a major component of the CDK8 kinase module. Pathogenic variations in *MED13L*leading to protein truncation are associated with a typical MED13Lsyndrome. The condition is mainly characterized by a global developmental delay a specific facial gestalt, minor cardiac and skeletal malformations.

Methods: We investigated the functional consequences of two heterozygous MED13L variations located at the canonical donor splice-site motif of exon 7: c.1009+1G>C and c.1009+5G>C. Initially, we took advantage of the predicting tool SpliceAI with varying parameters to assess splicing alterations. Subsequently, we conducted RNA studies of the splicing consequences using Sanger sequencing and quantitative PCR analysis. Both patients exhibited a clinical MED13L syndrome.

Results: The initial prediction of splicing impact, using a default window of 50bp for prediction calculation, suggested an exon 7 skipping, potentially resulting in the loss of the phosphodegron motif essential for MED13L regulation and degradation. However, a reanalysis of predictions with a larger window of 500bp for SpliceAI revealed a different potential outcome, indicating the activation of a cryptic donor site in intron 7. RNA analysis confirmed that both intronic variations c.1009+1G>C and c.1009+5G>C affected the exon 7 splice donor site, leading to the retention of 73 bp of the same intron. The retention induced a frameshift and premature transcription termination, explaining the phenotypic presentation. Contrary to the initial hypothesis of a shortened protein accumulation, the functional consequences were the production of a loss-of-function protein.

Conclusions: This study identifies a cryptic splicing donor site in MED13L intron 7, underscoring the importance of extending beyond initial predictions. The significant discrepancies between predictions and experimental results emphasize the need for cautious interpretation. Understanding the molecular consequences of these variations provides a comprehensive view of the functional impact of genetic variations associated with MED13L syndrome.

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Building meta-cohorts from copy number variant (CNV) carriers and their family members

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Copy number variants **(**CNVs) are implicated across many neurodevelopmental disorders. Currently, there is an unmet need: the creation of large meta-cohorts from CNV carriers to increase power in analysis. Building meta-cohorts is complex due to the following: many legacy datasets may share participants, may not be linked, and may have some but not all common measures. Internationally differences in consent, data-sharing agreements and data security between countries also may present challenges.

Initially the problem is **data findability.** Data does not necessarily need to be curated and pooled into one centralised database, rather it can be made findable by linking IDs across studies to de-duplicate meta-cohorts. Subsequently, minimal participant meta-data can be loaded onto a common platform, effectively 'advertising' the data. In this way researchers can build larger meta-cohorts through collaboration.

Currently we have legacy phenotypic data and DNA samples across five separate studies of neuro-developmental disorders (NDDs) from CNV carriers and controls. For many of the participants common phenotypic measures have been collected in separate databases. We have built a meta-cohort of over 1700 participants by building a database of ids for each participant (cross-id database), de-duplicating the meta-cohort, but leaving the original phenotypic data intact, thus creating local meta-data for each participant. Now, the meta-data, with global universal identifiers (GUIDs) is being loaded into a larger European federated database, **MINDDS-connect**, to contribute towards making a larger International meta-cohort.

Going forwards, we will make better use of legacy data in analysis and begin to derive better methods for collection, curation and storage of consent, phenotypic and genetic data for CNV carriers. This will aid in the efficient generation of large international meta-cohorts.

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ID 65

Functional characterization of variants in CACNA1A causing developmental epileptic encephalopathy, hemiplegic migraine, and ataxia

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Cav2.1 is a calcium channel with an important role in the communication between the neurons of the brain and at the neuromuscular junctions. Loss- or gain-of-function variants in the *CACNA1A* gene, which encodes the pore-forming subunit of Cav2.1, lead to a broad clinical spectrum including episodic and spinocerebellar ataxia, hemiplegic migraine, and developmental epileptic encephalopathy. To understand the functional consequences of *CACNA1A* variants, we utilize cell culture models of the four variants p.(Gly230Val), p.(Arg588Cys), p.(Ala712Thr), and p.(Ala1507Ser) identified in four unrelated affected individuals. Using whole-cell patch clamp to determine the effect of each variant on channel function, preliminary data show that the p.(Gly230Val) and p.(Arg588Cys) variants lead to loss-of-function, caused by reduced current density and a positive shift in the voltage-dependent activation of the channel, respectively. The electrophysiological consequences of the p.(Ala712Thr), and p.(Ala1507Ser) variants are currently being analyzed. As the general practice of seizure treatment is a trial-and-error approach with a great burden for the affected individuals and their families, functional knowledge of variants will facilitate clinicians' choice of the most relevant drugs, avoiding ineffective or even disease-aggravating treatments and adverse drug reactions. Out findings thereby contribute to the translation of the genetic diagnosis to treatment in line with the current paradigm of precision medicine.

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Alterations in cortical differentiation and neuronal network activity in 22q11.2 deletion syndrome

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22q11.2 deletion syndrome (22q11.2DS) or DiGeorge Syndrome is a rare neurodevelopmental disorder. It is characterised by a range of symptoms including heart defects, developmental delay, learning difficulties, and highly increased incidence of schizophrenia compared to the general population. Investigating the development of cortical neurons and their network activity will help us to identify molecular mechanisms that may lead to the various cognitive symptoms of 22q11.2DS. Induced pluripotent stem cell lines (iPSCs) were generated from both 22q11.2 patients and controls. These lines were differentiated into cortical neurons using a dual-SMAD inhibition protocol and characterised using immunocytochemistry. Once neurons were generated the network activity was measured using multi-electrode arrays. Results show changes at the iPSC stage, with 22q11.2DS lines showing a greater propensity towards spontaneous differentiation. Initial data also suggests changes in the expression of NPC markers in 22q11.2DS lines. Changes in neuronal network activity was also seen in the 22q11.2DS lines on multi-electrode arrays. Patient lines showed a change to the pattern of synchronised network activity similar to that previously seen in other neurodevelopmental disorders. The results suggest that changes in neuronal development may lead to changes in functional activity. Future works aims to determine molecular changes in the neurons that underpin the functional changes and to then use pharmacology to rescue the changes.

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- abstracts -

ID 5

Health care of persons with complex developmental disabilities from 3 european experiences: France, Italy, and Norway

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Background

The health care pathway of persons with complex developmental disabilities differs by country, depending both on the specificities of the associated health care system and the related societal views. In 2017, the French National Organization of Solidarity for Autonomy entrusted to a French expert group, a specific mission to analyse three European experiences.

Specific aim

The aim of this paper is to report the similarities and differences for health care pathway of persons with complex developmental disabilities between France and two other European countries, Italy and Norway. The 3 countries present different health policies and different ideologies for the care management of persons with complex developmental disabilities.

Method

A French group of 6 experts (including a neuro-paediatrician, an occupational therapist, a specialist of physical medicine and rehabilitation; a responsible member of a residential facility; a family caregiver representative; and the administrative coordinator of the French Polyhandicap Federation) travelled in Italy and Norway (3 and 4 days, respectively). Information was collected from standardized forms including dedicated structures, care delivery, dedicated physicians and other health care workers, human and financial aid, place of the caregivers, formations, preventive and therapeutic actions.

Findings

Law and health policies, funding, care coordination, and education differ between the three countries (France, Italy, and Norway) and have consequences on the life of the patients and their families.

Discussion

Three different society models for modalities of persons with complex developmental disabilities may have consequences on the life of the patients and their families. This work may help to optimize level of care according to both patient characteristics and family characteristics.

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ID 6

Persons with polyhandicap: Being cared for in a pediatric structure for young people over 18: is it really a problem?

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Context and aim

A dysfunctional transition process leads to adverse consequences in health in various chronic health conditions. Some French studies showed more than 10% of adults with multiple disabilities maintained in children's institutions, that can be considered inadequate. The aim of this study was to assess to what extent being cared for in a pediatric structure for young people over 18 is really a concern.

Method

This study was included in the French national polyhandicap cohort (EVAL-PLH) carryed out in 4 specialized rehabilitation centers and 9 residential facility structures. Two groups of young people with polyhandicap (18-35 years) were defined according to the structure where they were care managed: devoted to children vs adults.

Results

From the 204 young adults included in the second wave (2020-21), 67 (33%) were care managed in a pediatric structure. In comparison with the 67% of persons care managed for in structures devoted to adults, they were significantly younger, had a lower body mass index, had less often a puberty completed, presented a less severe health status (less comorbidities) and less behavorial disorders, and were less likely to be examined by general practitioner or physical medicine rehabilitation. However, the 2 groups did not differ on the: nature of the care structure (specialized rehabilitation centers or residential facilities), stability of health status, etiology, monthly prescribed sessions or gap between the number of prescribed and performed sessions (physiotherapy, psychomotor therapy)

Conclusions

While consumption of paramedical care did not differ between young adults care managed in structures devoted to adults or devoted to children, consumption of medical care differed. Optimization of the coordination between the 2 systems should improve the global care management.

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ID 7

Persons with polyhandicap: Could the presence of behavioral disorders be the cause of a greater isolation?

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Context and aim

Behavioral disorders are very frequent in children with polyhandicap (40-70% according to the various studies) and largely increased during adulthood. The presence of noisy behavioral disorders may have an important consequence for the family by encouraging them to choose a non-family care structure and for the health care team by reducing the spectrum of health care provision and psychosocial education. The aim of this study is to assess the consequences of the presence of noisy behavioral disorders on the care provision and psychosocial education.

Method

This study was included in the French national polyhandicap cohort (EVAL-PLH) carryed out in 4 specialized rehabilitation centers and 9 residential facility structures. Noisy behavorial disorders were defined by the presence of at least one of the following items: including intermittent screaming, intermittent crying, agitation, self-aggressivity and hetero-aggressivity.

Results

From the 614 persons included in the second wave (2020-21), 71% presented at least one noisy behavorial disorders (NBD). In comparison with the 29% of persons without NBD, they were significantly older, were more frequently cared managed for in specialized rehabilitation centers (than residential facilities), enjoyed outings outside less often, were less visited by the family, and returned home less often. Physiotherapy, occupational therapy, and psychomotor therapy were less often required-prescribed for the persons with NBD in comparison to the persons without NBD.

Conclusions

The presence of noisy behavioral disorders in persons with polyhandicap could be the cause of a greater isolation: more distant links with the families and narrower range of care.

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ID 8

Development and initial validation of the polyhandicap severity scale

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Objectives

Providing a new tool, based on the point of view of experts in polyhandicap, which assesses the global severity of the health status of polyhandicapped persons is necessary. We present herein the initial validation of the polyhandicap severity scale (PSS).

Methods

The initial development of the tool was undertaken in two steps: item selection and validation process. The final set included 10 items related to abilities and 17 items related to comorbidities and impairments. The patient selection criteria were as follows: age > 3 years, age at onset of cerebral lesion under 3 years old, with a combination of motor deficiency and profound intellectual impairment, associated with restricted mobility and everyday life dependence. External validity, reproducibility (20 patients), responsiveness (38 patients), and acceptability were explored.

Results

During the 18-month study period, a total of 875 patients were included. Two scores were calculated: an abilities score and a comorbidities/impairments score (higherscore, higher severity). The 2 scores were higher for: older patients, patients with a progressive etiology, patients with more devices and more medications, patients with higher dependency and lower mobility. Indicators of reproducibility and responsiveness were satisfactory. The mean time duration of fulfilling was 22 minutes (standard deviation 5).

Conclusions

Quantifying the health severity of polyhandicapped persons is necessary for both healthcare workers and health decision makers. The polyhandicap severity scale provides the first reliable and valid measure of the health severity status for children and adults.

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Persons with polyhandicap, their families, and the institutional caregivers: the french EVAL-PLH cohort

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Introduction

The optimization of care management for persons with polyhandicap and their caregivers is possible with increasing knowledge of the condition's clinical characterization and care trajectories and the experiences, beliefs and representations of caregivers. From this perspective, and to improve the knowledge about this population of patients, their specific needs and the impacts on their caregivers, the French prospective cohort study, EVAL-PLH (EVALuation PoLyHandicap) study, was implemented.

Method

This is a prospective cohort study. Thus far, data have been collected at 2 points. The first part of the study was organized between 2015 and 2016, and the second part was organized between 2020 and 2021. The cohort involved persons with severe polyhandicap who were cared for at reeducation centres, residential facilities, and specialized paediatric/neurological departments. Three different populations were eligible: i. persons with severe polyhandicap; ii. familial caregivers of the included persons; and iii. institutional caregivers of the included persons. Data were collected from the patients' records and from self-reported questionnaires fullfilled by caregivers.

Results

The first wave (2015-2016) included persons with polyhandicap, 440 familial caregivers, and 362 institutional caregivers. The second wave (2020-2021) included 624 persons with polyhandicap (comprising 492 cases assessed at the 1st wave), 226 familial caregivers, and 223 institutional care. International publications have described the following: the clinical characteristics and health status of persons with polyhandicap, the adequacy of the care management, and the psychobehavioural issues of familial and institutional caregivers. Additional funding has been received for ancillary studies : the POLYMIME study and the PolyAGE study (familial impact of polyhandicap using mIxed method approach). The POLYRENE group (POLYhandicap: the French REsearch NEtwork) aimed to improve the visibility of the cohort.

Conclusion

The third wave is planned for 2025-2026. The longitudinal approach provides more valid information than cross-sectional studies, allowing to better understand the observed phenomena and explore the dynamics and modelling sequences between them.

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How can we improve outpatient care for children with PIMD? Insight into experiences and preferences of parents and healthcare professionals

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Background: Children with profound intellectual and multiple disabilities (PIMD) have extensive and intensive needs for care, due to their severe intellectual and motor disabilities with increased risk for complications such as pulmonary infections. The involvement of multiple healthcare professionals (HPs) can lead to an unclear and inconsistent treatment plan for all involved. This study aims to give insight into the care needs of children with PIMD, focusing on medical needs and organisation of (outpatient) care, by conducting qualitative research on the experiences and preferences of parents of patients with PIMD and HPs.

Methods: For this study, a mirror meeting with six parents of children with PIMD was conducted. Additionally, we performed semi-structured interviews with six external HPs. The data were analysed using the framework method.

Results: Four themes have been identified (patient care, communication, family experience, external network). Parents and HPs miss care coordinators, the task division between the involved HPs should be clear, and the transition to adult care should be prepared properly. Effective exchange of information is necessary for everyone involved to know what to do. Awareness of the emotional toll on parents is important. Furthermore, HPs consider multidoctor appointments as helpful, while parents think this might be too much for their child.

Conclusions: This study provides insights into the challenges and essential aspects of care for children with PIMD, aiming to enhance the organisation and effectiveness of (outpatient) care in the future. Based on the result, an overview of recommendations for daily practice is presented in Figure 1.

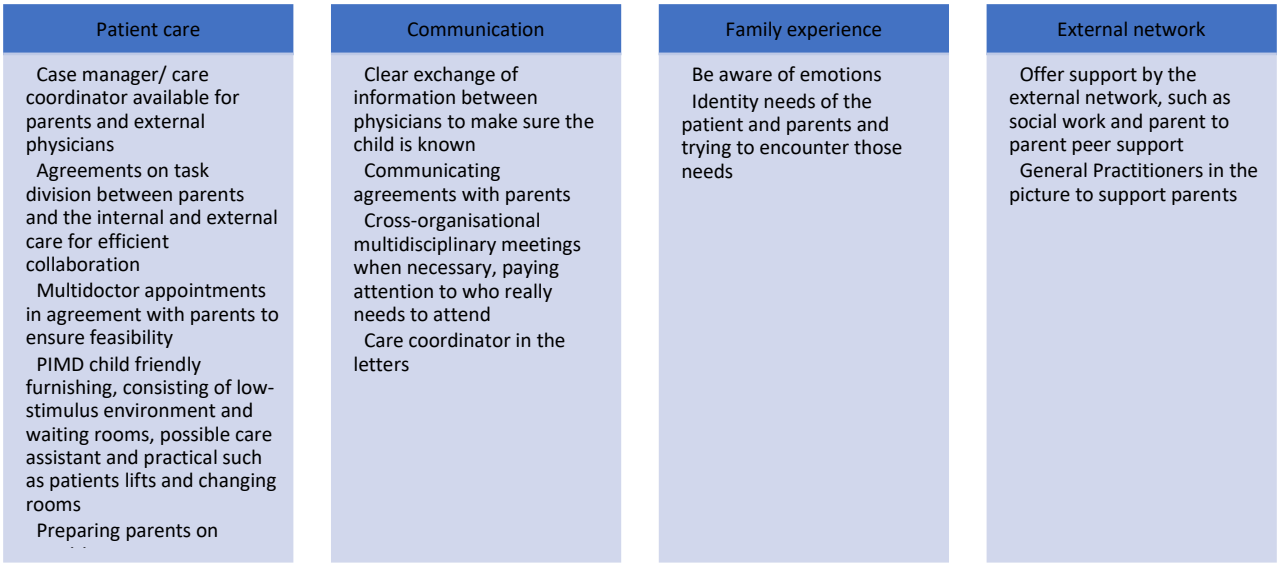

Figure 1: Implications for daily practice. Abbreviation: PIMD, profound intellectual and multiple disabilities.

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Parents' experiences of parenting a child with profound intellectual and multiple disabilities in France: a qualitative study

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Introduction: Parents of persons with profound intellectual and multiple disabilities (PIMD) play a major and often lifelong role in the care and support of their child. A better understanding of parents' perspectives regarding their experiences of parenting their child with PIMD is essential to support them more effectively. Although this topic has been explored extensively in Anglo-Saxon and Northern European countries, little is known about the experience of these parents in a highly institutionalized context such as that in France.

Objective: We explored parents' experiences of the activities they performed to care for their child with PIMD (namely, the "parenting work") in the French context.

Method: Qualitative semistructured interviews were conducted by telephone with 34 parents of persons with PIMD aged 8 to 35. The resulting data were analyzed using thematic analysis.

Results: The analysis highlighted the diversity of activities performed by parents as well as the influence of context on the forms of this parenting work. Five themes were developed: (1) navigating the challenges of obtaining medical recognition; (2) negotiating a concealed domain and becoming an expert; (3) unfolding medical and medico-social care management; (4) navigating the challenges of daily living; and (5) shaping one's child's possibilities.

Conclusion: This study offers a better understanding of the challenges, levers, and expectations of parents of children with PIMD in France. Contextual factors such as the lack of knowledge of PIMD among health professionals, access to knowledge and know-how associated with care management, the administrative complexity of access to care and equipment, institutional issues (e.g., professional turnover) and societal ableism (e.g., access to infrastructures, interpersonal discrimination) shape the work parents perform to support their child's needs. It is necessary to consider contextual aspects to better support these parents and their children.

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(author adapted the title)

Gaps in transitional care for adolescents with profound intellectual and multiple disabilities in the Netherlands: experiences of health care professionals and parents.

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Introduction: Background & purpose. Due to increasing medical possibilities, more adolescents with profound intellectual and multiple disabilities (PIMD) are reaching the age of 18. They then have to make the transition from pediatric to adult care. Due to their complex condition this transition can be stressful for parents. Little is known about how healthcare professionals in the Netherlands secure the quality of their transitional care to this particular patient group. The aim is to identify factors influencing the quality of this transition.

Methods. Semi-structured interviews were conducted with 20 health care professionals in pediatric and adult care (medical doctors and nurse practitioners) from various medical specialties. Interviews were thematically analyzed using both open and deductive analysis techniques. A member check using a structured checklist was performed. Seven parents of adolescents with PIMD - who had already gone through the process of transition - took part in a focus group, in which they compared the outcomes of the interviews with their personal experiences on transitional care. Thematic analysis was used for this focus group.

Results. Transitional care for adolescents with profound intellectual and multiple disabilities involves more than just medical transfer, but encompasses difficult decisions around daycare, housing, financial compensations and legal aspects. Analysis showed a variety of transitional care practices. Health care professionals emphasize that transition in this patient group is challenging due to the fact that adolescents have to make multiple transitions to multiple health care professionals.

Influencing factors on quality of transitional care are:

- *Health care professionals*

Affinity with and communication skills for interaction with (families of) people with profound intellectual and multiple disabilities, knowledge of various syndromes, having a holistic view on practicing medicine, timely addressing the topic of transition, knowledge of social, political and legal factors;

- *Organization of health care*

Financial constraints funding (joint) consultation, shortage of physicians for intellectual disability, communication and coordination difficulties when physician intellectual disability – who are usually not employed by the hospital – wants to admit a patient to the hospital;

- *Adolescent with PIMD and family*

Families with limited health literacy and/or language barrier, shared decision making.

Parents of adolescents with profound intellectual and multiple disabilities confirm these results and emphasize the need for improvement of this process.

Discussion & conclusion. Transitional care is particularly complicated for people with profound intellectual and multiple disabilities due to multiple health problems, reliance on others for interaction and collaboration with health care professionals and the lack of a coordinating practitioner in adult care, such as the pediatrician in pediatric care.

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Focusing on what is important in severe neurological impairment- a prioritisation survey of parents and professional caregivers

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Introduction

Children with severe neurological impairment (SNI) have complex medical care needs as well as motor and cognitive impairment, leading to frequent interactions with healthcare and disability services. The aim of this study was to explore what is important to family members and professional caregivers of children with SNI, by asking what they think researchers should be trying to answer and what services should consider.

Participants and methods

An anonymous online survey was developed based on a three- question James Lind Alliance prioritisation survey, with permission. The survey was administered through a combination of social media dissemination and through a community service provider and school for children with complex needs and neurodisability. The survey was open to family members and professional caregivers of children (0-18 years) with severe neurological impairment.

Results

The results centred on child-focused (diet, medication, symptom management, fatigue, pain, tone, comfort, toys and communication), parent-focused (guilt, burnout, worries about the future, peer support), family-focused (impact on siblings and family as a whole) and service-focused (access to specialist care and support, equipment, having to fight for everything, acute care, best-practice guideline application, differing opinion, caseloads, transition) questions.

Conclusion

Parents of children with severe neurological impairment have many concerns about their child and their child's condition across four key domains; their child, themselves, their family and services. Researchers and providers of services for these children and their families should consider all of these domains and how they interact with each other.

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Tacit knowledge in the care for persons with profound intellectual and multiple disabilities

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Background:

Since persons with profound intellectual and multiple disabilities (PIMD) cannot clearly communicate their needs and preferences, caring for them demands specific expertise. Parents and professional caregivers need to interpret and attune to a person's subtle idiosyncratic cues and bodily signs to assess their well-being and together perform everyday care routines. They talk about this specific ability as 'reading' or 'hearing' a person' or 'sensing' their needs. Scholars use the term 'tacit knowledge' to describe this personal, embodied kind of knowing that often remains implicit, and that is difficult to explicate or pass on to others. As little is known about the tacit knowledge of parents and professional caregivers of persons with PIMD, in our research project we aim to explore its nature, including what is necessary for its development and transfer.

Methods:

We conducted an interpretative synthesis of the literature, held semi-structured interviews with professional caregivers, ID-physicians, and parents of persons with PIMD, and audio-taped consultations with ID-physicians.

Results:

In a trilogy we will give an overview of the research project in which tacit knowledge is conceptualized as paramount in providing good care for persons with PIMD. First, we will present the findings of our literature review on the nature and development of tacit knowledge between persons with PIMD and their professional caregivers. Secondly, we will present the findings of our interview study with parents, in which we explore how parents build, use, and potentially share their tacit knowledge of their child with PIMD. Thirdly, we will discuss our qualitative research findings analyzing audio-taped consultations with ID-physicians with parents of patients with PIMD to explore how tacit knowledge is brought forward and how its content, form and function is considered between parents and physicians. Furthermore, we will present our findings from semi-structured interviews with ID-physicians to explore their perceptions of tacit knowledge during consultations and in medical care for people with PIMD,

Discussion:

Based on our findings, we will reflect upon the implications of thinking in terms of tacit knowledge for the care for persons with PIMD, including medical care.

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Meet our scientific & organizing committee

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).

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.

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.

Lina Ramos is a clinical geneticist, Medical Genetics Unit of ULS Coimbra, Portugal, with a special interest in dysmorphology (pre and postnatal period) and genetic neurodevelopment disorders. She is an associate professor of the Faculty of Healthy Sciences, University of Beira Interior. She coordinates de HPC of ITHACA ERN in Coimbra and is a member of the working group on NDD. She is the president of the College of Medical Genetics in the Portuguese Medical Association.

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.

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.

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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.

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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With support of In-Act Marketing & Organization B.V. and It's Comunicação & Eventos

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