Abstract book

Poster presentations

EuroNDD 2023

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

April 20-21, 2023, Amsterdam

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Syndromic intellectual disability in Tunisian patients: contribution of next generation sequencing

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Background: Intellectual disability (ID) is one of the major public health problems. It could be isolated or syndromic (SDID). In the latter case, when a clinically or genetically heterogenous syndrome is suspected or there is no clinical guidance, confirming the genetic diagnosis requires the use of Next-Generation Sequencing (NGS).

The aim of our work was to illustrate the contribution of NGS in determining the genetic diagnosis of SDID in Tunisian patients.

Methods: This study was retrospective and included patients followed-up for SDID at the department of congenital and hereditary diseases of Charles Nicolle hospital in Tunis over a period of 24 years, from 1996 to 2020. A molecular study was performed using NGS.

Results: Thirty-one patients, from 30 families, were enrolled in our cohort. The sex-ratio was 0,82 (14/17) and the average age at the first examination was 4,13 years. Consanguinity was found in 47% (14/30) of the cases and family history of ID was reported in 17% (5/30). They were mainly referred because of dysmorphic features (22/31). They all had ID (31/31) associated to developmental delay (18/31), behavior disorders (14/31) and epilepsy (4/31). Clinical examination showed dysmorphic features (31/31), growth disorders (24/31), extremities abnormalities (14/31) and neuromuscular or motor abnormalities (11/31). Investigations revealed ocular anomalies (18/31), hearing impairment (7/21), skeletal abnormalities (8/12), heart defects (10/21), cerebral anomalies (12/23) and a metabolic disorder (1/10). Molecular studies were performed in all patients using Targeted Gene Panels (TGP) (24/31), Whole Exome Sequencing (WES) (7/31) and Whole Genome Sequencing (WGS) (1/31). One patient had both TGP and WGS. A genetic diagnosis was established using NGS in 67% (20/30) of these families. This allowed genetic counseling then prenatal diagnosis in two of them revealing a healthy fetus in one case.

Conclusion: Our results illustrate the contribution of NGS in establishing the genetic diagnosis of SDID, as it achieved a diagnostic yield of 67%. This was a key to better management and adequate genetic counseling. Thus, we could perform cascade screening and prenatal diagnosis.

However, patients with negative results should be further explored.

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Reanalysis of SNP analysis data in patients with neurodevelopmental delay

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The number of genes known to cause intellectual disability is increasing every year. In the past 6 years, about 500 new genes were discovered to cause intellectual disability.

This has implications for the diagnostic process in neurodevelopmental delay (NDD). After a negative result it pays off to run a re-analysis after some time. Indeed several groups have studied the yield of re-analysis of WES-data for several indications, reporting a mean yield of ~15%.

The growing knowledge about disease-causing genes also has implications for the interpretation of Copy Number Variants (CNVs). Around 20% of individuals with intellectual disability have a CNV, in a total of 10-12% this CNV is classified as likely pathogenic. This leaves a substantial number of (de novo) CNVs with unknown significance.

Our laboratory switched from karyotyping to CNV analysis in 2008, and has since collected a series of ID patients with de novo CNVs that could not be classified.

A recent case of re-classification of a de novo CNV as pathogenic, made us realize that the growing knowledge about disease-causing genes also has implications for CNVs. This led us to study all ID patients between 2008-2013 with a de novo CNV (n=107). We re-evaluated CNVs with the label *possibly pathogenic* or *unlikely pathogenic* by checking location and gene content in both PubMed and DECIPHER.

In 50% of cases we found recent publications about the CNV. We could re-classify previously unclassifiable variants in 17% of patients. In 7% this had clinical consequences (e.g. screening advise).

We will present our data collection and show clinical examples of re-classified CNVs.

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Clinical practice guidelines for rare genetic neurodevelopmental disorders: a review and systematic quality appraisal

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Introduction: Patients with rare genetic neurodevelopmental disorders are often affected with intellectual disability and complex multi-organ comorbidity, requiring lifelong and multidisciplinary care. To optimize care for this population, effective sharing and application of knowledge are indispensable. Clinical practice guidelines (CPGs) are central to evidence-based medicine as they bridge the gap between scientific evidence and clinical practice. Yet, it is challenging to develop CPGs for this population and no systematic evaluation of the number and methodological quality of existing guidelines has been conducted.

Methodology: A systematic search of MEDLINE and EMBASE, in combination with a search of all Orphanet disorders classified as 'rare genetic intellectual disability' (ORPHA:183757), is conducted to identify existing CPGs and similar quality documents for (rare) genetic neurodevelopmental disorders. In addition to a descriptive analysis of CPG characteristics, methodological quality is assessed using the AGREE (Appraisal of Guidelines, Research and Evaluation) II tool, consisting of the following domains: scope and purpose; stakeholder involvement; rigour of development; clarity of presentation; applicability; and editorial independence.

Results: Results are in development and will be presented at the EuroNDD meeting.

Discussion: This review will summarize the current state of affairs regarding the availability and quality of CPGs for rare genetic neurodevelopmental disorders to provide recommendations for future CPG development, improving evidence-based care for patients with rare genetic disorders and/or intellectual disability.

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Cannabidiol (EPIDYOLEX) for behavioral problems in patients with Tuberous Sclerosis Complex, Sanfilippo Disease and Fragile X Syndrome: protocol for a series of randomized placebo-controlled N-of-1 trials; can we make personalized care for individuals with an intellectual disability happen? Insights from a large intellectual disability registry

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Introduction: Behavioural problems in rare genetic neurodevelopmental disorders (RGNDs) are often refractory to regular psychological or pharmacological treatment. Anecdotal reports from families describe a significant improvement in behavioural manifestations by using cannabis or cannabidiol (CBD) oil. Our objective is to examine the effectiveness of CBD on irritability and other behavioural manifestations in individuals with Tuberous Sclerosis Complex (TSC), Fragile X syndrome (FXS) and Sanfilippo disease, proposing an alternative trial design since traditional randomized controlled trials (RCTs) are complex in patient populations that are rare and heterogeneous.

Methods: We aim to conduct a placebo-controlled, double-blind, randomized, multiple crossover N-*of*-1 study in 30 children and adults aged ≥6 years with genetically confirmed TSC, Sanfilippo disease or FXS diagnosis and suffering from severe behavioural manifestations, based on a power analysis. The treatment is oral CBD (Epidyolex) up to a maximum of 25 mg/kg/day, twice daily. The primary outcome measure is the subscale irritability of the Aberrant Behavior Checklist (ABC). Secondary outcomes include other psychiatric and behavioural manifestations, quality of life, disease-specific outcomes, parental stress, personalized outcomes, seizure frequency, and side effects. Statistical analysis includes a mixed model analysis. All subjects receive an assessment of their individual treatment effect and data will be aggregated to investigate the effectiveness of CBD for behavioural manifestations in TSC, FXS and Sanfilippo at a group level.

Conclusions: This N-*of*-1 trial is targeted to an unmet medical need and will provide information on the effectiveness of CBD for behavioural problems in multiple disorders, generating generalizable knowledge at a RGND population level. This protocol can be used as an example to empower other researchers to conduct N-*of*-1 studies, providing a much-needed bridge between science and practice to optimize evidence-based and personalized care.

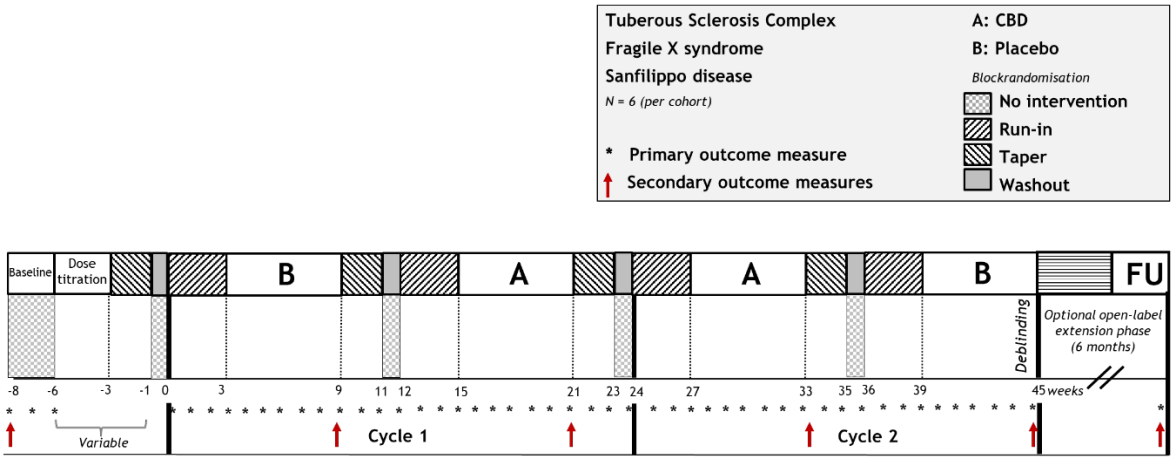

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Figure. N-of-1 design to study the effectiveness of cannabidiol (CBD) in Tuberous Sclerosis Complex, Fragile X syndrome, and Sanfilippo disease.

miRNAs and isomiRs: serum-based biomarkers for the development of Intellectual Disability and Autism Spectrum Disorder in Tuberous Sclerosis Complex

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Tuberous sclerosis complex (TSC) is a rare multi-system genetic disorder characterized by high incidence of epilepsy and neuropsychiatric manifestations known as tuberous-sclerosis-associated neuropsychiatric disorders (TANDs), including autism spectrum disorder (ASD) and intellectual disability (ID). MicroRNAs (miRNAs) are small regulatory non-coding RNAs that regulate the expression of more than 60% of all protein-coding genes in humans and have been reported to be dysregulated in several diseases including TSC. Recently, miRNA levels in serum have received increased attention as non-invasive biomarkers. Given the broad spectrum of TANDs at a behavioral, psychiatric, intellectual, neuropsychological level, identification of these biomarkers can aid in the early prediction of neuropsychiatric comorbidity development, resulting in early intervention. Thus, in the current study, RNA-sequencing analysis was performed to evaluate miRNA expression patterns in serum of infant TSC patients (aged 0-3 months). A Receiver Operating Characteristic (ROC) curve analysis was used to identify circulating molecular miRNA biomarkers able to discriminate the development of neuropsychiatric comorbidity, either ASD, ID or both, in infant patients with TSC. Verification of biomarker potential was performed using RT-qPCR for the identified miRNAs. This study identified multiple promising miRNA biomarkers for the early prediction of ASD, ID or both in young TSC patients and verified the possible use of RT-qPCR for miRNA expression levels from serum. Moreover, these results show that miRNA expression could potentially predict the development of ASD and ID in TSC patients before formal psychological evaluation can take place. With this, our results support the notion that circulating miRNAs have the potential to aid standard clinical testing in the early risk assessment of ASD and ID development in TSC patients. With this, parents could learn to improve their children's behavioral and social skills and reduce the impact of these comorbidities on their quality of life.

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GenIDA, an international participatory database to better characterise comorbidities of genetic forms of intellectual disability: novel findings on Koolen-de Vries syndrome

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GenIDA is an international online research project initiated to better characterise the clinical manifestations and natural history of genetic forms of intellectual disability with or without 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 major physiological functions, etc. Five open-ended questions explore families' perception of the events that most affect their relative's health and quality of life, the secondary effects of treatments, etc. Currently, the questionnaire is available in 7 languages and has been completed for over 1670 patients, the main cohorts being Koolen-de Vries/KdVS (n=249) and Kleefstra/KS (n=191) syndromes. Analysis of the data collected for 237 individuals with KdVS was conducted and showed no significant differences between patients with KdVS caused by a deletion of 17q21.31 and those with a pathogenic variant in KANSL1. GenIDA findings on KdVS were consistent with the existing literature and revealed a previously unreported susceptibility of these patients to respiratory problems (recurrent pneumonia, childhood asthma). The reported frequency of epilepsy is consistent with data from the medical literature, but GenIDA data analysis provided further information on the nature of the seizures associated with KdVS, as well as information on the efficacy and possible adverse effects of the anti-epileptic treatments used. Comparative results on KS, DDX3X (n=50), KBG(n=48) and MED13L (n=45) cohorts regarding notably sleep and epilepsy aspects will also be presented. These results validate the interest of our participatory approach: through their direct involvement, families can reveal aspects of the pathology that were previously underestimated, and thus lead to the implementation of incidental studies on specific aspects of rare forms of ID.

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"Dysmorphology Meeting" – An MDT Approach To Improve Access To The Clinical Genetics Services

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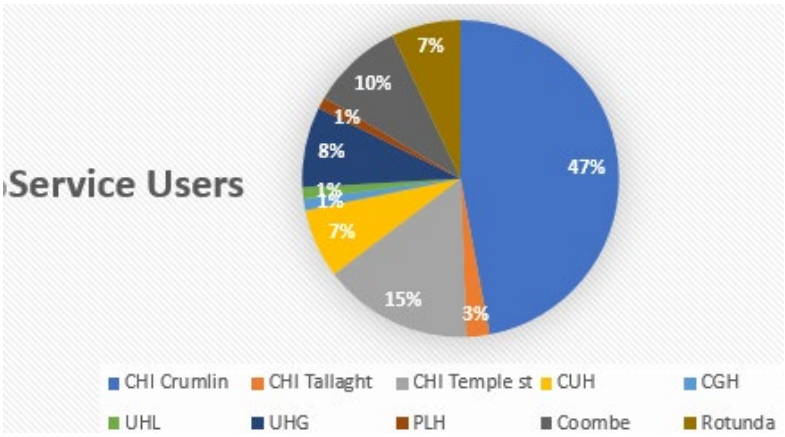
Background: The clinical genetics service in the Republic of Ireland remains an oversubscribed service with prolonged waiting times. (1). An inability to provide urgent in-patient consultations, because of consultant shortages, led to us commencing an online weekly advisory dysmorphology meeting. The aim was threefold: 1) help with diagnoses, 2 as give advice to families via the referring physician and 3 give advice on the most appropriate test.

Objectives: To implement a weekly multidisciplinary dysmorphology meeting. To evaluate the meeting demographic and outcome.

Methods/Interventions: The virtual meeting runs each working Monday. Cases are logged on the genetics database. The requesting team present a brief synopsis of the patient and photographs. The clinical genetics team (4 consultants and 2 registrars) comment on cases and provide advice. A written closing recommendation from the clinical genetics team is provided.

We retrospectively audited the discussed cases over an 18 month period from 01/04/2021 to 01/10/2022.

Findings: 85 clinical cases were reviewed in 44 clinical meetings. The mean number of cases per meeting was 1.8 (median = 2, range 1-6). Referrals were received from 21 different speciality teams across 10 hospital sites. 55/85 (64%) of referrals were from within CHI hospitals (40 from CHI @ Crumlin). The largest referral speciality was neonatology (52% of referrals).



The benefits of the meeting include ability to 1) offer prompt advice to (often critically) ill children, 2) ensure the most appropriate test is ordered, 3) ensure more efficient use of a scarce resource- consultant time, 4) get advice from all 4 genetic consultants as opposed to a single opinion.

Future Plans: This project is an innovative example of how MDT collaboration can improve access and quality of care. We will continue to encourage clinicians (especially from outside Dublin) to avail of this service and reduce inequity of care across the Irish Republic.

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References: 1. Lynch, SA., Review of the Clinical Genetics Medical Workforce in Ireland, 2019, HSE 2019 Accessed at: hse.ie/eng/staff/leadership-education-development/met/plan/specialty-specific-reviews/clinical-genetics-2019.pdf on 08/09/2022.

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Parents as partners: data consistency and data availability of parent-reported phenotypes

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Even with the introduction of new genetic techniques that enable accurate genomic characterization, knowledge about the phenotypic spectrum of rare chromosomal disorders remains limited, both in literature and existing databases. Yet this clinical information is of utmost importance for health professionals and the parents of children with these rare diseases.

Since existing databases are often hampered by the limited time and willingness of health professionals to input new data, we collected phenotype data directly from parents of children with a chromosome 6 disorder. Parents were reached via social media, and their information was collected via the online Chromosome 6 Questionnaire, which includes 115 main questions on congenital abnormalities, medical problems, behaviour, growth and development and is available in seven different languages.

To check whether the parent-reported phenotypes were reliable for research purposes, we assessed data consistency by comparing parent-reported phenotypes to phenotypes based on copies of medical files for the same individual. Besides, we studied data availability by comparing the data available on specific characteristics reported by parents to data available in the existing literature.

This is the first study to compare phenotype data collected directly from parents to data extracted from medical files on the same individuals. We found that the data was highly consistent. The reported answers to the main questions on phenotype characteristics were 85–95% consistent, and the consistency of answers to subsequent more detailed questions was 77–96%. For all but two main questions, significantly more data was collected from parents via the Chromosome 6 Questionnaire than was currently available in literature. For the topics developmental delay and brain abnormalities, no significant difference in the amount of available data was found. The only feature for which significantly more data was available in literature was a sub-question on the type of brain abnormality present.

Our study shows that parent-reported phenotypes are very reliable and we encourage active patient and/or parent participation in data collection for all research on rare diseases.

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Can we make personalized care for individuals with an intellectual disability happen? Insights from a large intellectual disability registry

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Introduction: Technological advances have contributed to the rapid progress in identifying genetic causes of intellectual disability (ID). There is increasing knowledge about the phenotype and treatments for genetic disorders. However, it is unclear to what extent the genetic diagnosis is integrated into multidisciplinary ID care. Knowledge about a genetic etiology can contribute to understanding, preventing and treating physical and mental health manifestations. The aim of this study was to investigate to what extent information on the genetic etiology was actually part of multidisciplinary ID care, and to identify factors that were associated with integration of the genetic diagnosis in ID care to increase disorder-specific, personalized care.

Methods: The client database of 's Heeren Loo, a care organization for people with ID, was used to obtain a randomly selected proper sample of the ID population, consisting of 374 (2.5%) out of 14,549 clients of all ages. Subsequently, data on genetic diagnosis, clinical and demographic characteristics, types of support and care budget categories were systematically collected from medical records and files used by behavioral scientists, psychologists, and professional caregivers. The primary study parameter was the proportion of medical files, psychological/behavioral therapists files and files used by professional caregivers with a documented genetic diagnosis. In addition, patient characteristics and other factors that could be associated with presence on the genetic etiology were explored, using logistic regression analysis.

Results: Genetic test results were available for 148 (40%) of the 374 individuals with ID, with the genetic etiology reported by the care provider as causative for the ID in 80 (54%) of these individuals. Information on genetic etiology was documented in medical files (93%), psychologists/behavioral therapists files (29%), and files of professional caregivers (68%) when involved. Level of ID, age and the legal representative's relationship to the patient (e.g., family member or professional) contributed most to the predictive model for factors associated with presence of information on the genetic etiology.

Conclusion: We explored the largest ID registry used in the Netherlands, and found that information on genetic etiology has often not been documented by various types of health care providers. Furthermore, we identified factors associated with presence of information on genetic etiology, possibly indicating inequality of access to genetic testing. Education on the importance of knowledge on the genetic etiology of ID for all types of health care professionals may increase empowerment of the patient, family members and care providers, and improve quality of multidisciplinary personalized care.

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Clinical pathways in rare diseases- cancer screening in PTEN hamartoma tumor syndrome in Portugal

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Deleterious heterozygous variants in *PTEN* cause a multisystem complex disorder, *PTEN* hamartoma tumor syndrome (PHTS), associated with high risk of neurodevelopmental disorders, malignancy, macrocephaly, benign tumors, skin, and endocrine disorders. As a complex rare disorder, it is important that patients are followed up by professionals with knowledge and training in the physical examination of PHTS, and who are aware of the specific cancer screening guidelines for this disorder.

To understand who is performing the cancer screening of PHTS patients, and to plan the training of professionals on this rare disorder, we analyzed the clinical screening pathway of a cohort of PHTS patients followed by three Medical Genetics departments in Portugal.

Our population from three Medical Genetics departments includes 24 patients from 17 families of which 12 were adults. Two adult patients were diagnosed with cancer, one male with thyroid cancer at the age of 26 years, and a female with bilateral breast cancer and papillary thyroid cancer by the age of 38 years.

In Center I, five patients, aged between five and 13 years old, did not initiate a cancer screening program. Seven minors already started cancer screening, all for thyroid cancer, in the other two centers. All adults were in a cancer screening program. In Center I, cancer screening was performed in three patients by their family doctor and non-oncologist hospital based-specialist, and for five patients by a non-oncologist hospital-based specialist. In Center II, one patient was only screened by her family doctor, and six patients were by non-oncologist hospital-based specialists. In Center III, all patients were screened by an oncologist.

Our data shows that who performs PHTS cancer screening varies between medical centers and even by patients in the same hospital. In addition, it shows the broad range of medical professionals involved in the cancer screening of PHTS patients, stressing the need for training of multiple professionals in PHTS, and multidisciplinary collaboration.

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Irritability in children with rare neurodevelopmental copy number variants (ND-CNVS)

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Background: Rare neurodevelopmental copy number variants (ND-CNVs) have been associated with high risk for neurodevelopmental and psychiatric conditions. Severe irritability is one of the most common reasons for referral to mental health services in the general population, and it is frequently seen in neurodevelopmental disorders such as those seen in children with ND-CNVs. Despite this, there remains a sparsity of studies investigating the presentation of irritability in children with rare ND-CNVs.

Aims: To investigate whether there is a difference in irritability in rare ND-CNV carriers compared to typically developing controls and to what extent irritability may be associated with other psychiatric diagnoses, and cognitive ability (IQ).

Method: 548 ND-CNV carriers (64.6% male, mean age 9.8 years), and 164 non-carrier, sibling controls (53% male, mean age 10.8 years) were recruited through Medical Genetics Clinics in the UK as well as rare disorder support charities and were deep-phenotyped in the CNV Research Group at Cardiff University. Irritability and psychopathology were assessed by primary caregiver report in children, age 7-17, using the research diagnostic Child and Adolescent Psychiatric Assessment (CAPA). Data from the CAPA was used to derive a dichotomous clinical irritability score, and to determine dichotomous DSM-V psychiatric diagnoses which were used in analysis. In a somewhat smaller sample of 479 carriers and 159 controls, Intelligence quotient (IQ) was also assessed using the Weschler Abbreviated Scale of Intelligence (WASI). Analysis included binomial logistic regression to investigate whether CNV status, age and gender predicted the presence of irritability. We also constructed models where irritability was predicted by psychiatric diagnoses, and cognitive ability.

Results: ND-CNV carriers had higher rates of clinical irritability than non-carrier, control siblings (54% of CNV carriers met threshold for irritability, compared with 20% of controls, $\chi^2(1)$ 8.219, p<0.001). CNV status predicts irritability when controlling for age and gender (OR = 4.38, CI = 2.91–6.77, p <0.001) . Males were more likely meet the threshold for irritability criteria than females (OR = 0.67, CI = 0.49–0.93, p <0.05). Attention deficit hyperactivity disorder, anxiety and oppositional defiant disorder were associated with irritability, however, when controlling for these diagnoses , ND-CNV status still predicted irritability (OR = 2.36, CI = 1.50 – 3.77, = p <0.001).

IQ was correlated with irritability in the sample (FSIQ: r (636) = -0.14, p = <0.001, PIQ: r (636) = -0.11, p < 0.005, VIQ: r (636) = -0.14, p = <0.001). However, when controlling for age, gender and psychiatric diagnoses, IQ did not predict irritability in rare ND-CNV carriers (FSIQ: (OR = 1.01, CI = 0.99–1.03, p = 0.44, PIQ: OR = 1.01 , CI = 0.99–1.01, p = 0.63, VIQ: OR = 1.01, CI = 0.99–1.01, p = 0.45).

Conclusions: Irritability is an important aspect of the phenotypic picture in children with rare neurodevelopmental CNVs and cannot simply be attributed to IQ impairment, or the presence of other psychiatric diagnoses. Thus, clinical irritability warrants further investigation as a potential transdiagnostic feature in children with ND-CNVs, in order to inform interventions for irritable behaviour in children with ND-CNVs.

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Autism symptom profiles in children and young adults with Fragile X Syndrome, Neurofibromatosis type 1, Tubereus Sclerosis Complex and Angelman Syndrome.

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Background: Studies have shown that autism spectrum disorder (ASD) prevalence rates are elevated in monogenetic syndromes, including Fragile X syndrome (FXS), Angelman syndrome (AS), Tuberous Sclerosis Complex (TSC) and Neurofibromatosis type 1 (NF1). Although the ASD phenotype shows overlap between syndromes, there are also clear differences, and even within syndromes individual differences are evident. This study aimed to identify ASD symptom profiles in a large group of children and young adults with FXS, AS, TSC and NF1.

Methods: Data on ASD symptomatology (Autism Diagnostic Observation Scale (ADOS-2) & Social Responsiveness Scale (SRS-2)) was collected in patients with FXS (n=63) AS (n=95), TSC (n=116) and NF1 (n=290). To identify groups of individuals with similar ASD profiles, we performed two latent profile analyses. We then used k-means clustering to methodologically validate our findings. We compared clinical characteristics for the latent profiles and performed exploratory analyses to investigate the association between the latent profiles and syndrome group, sex, IQ, and age.

Results: A four-profile model was identified as best fit for the ADOS, with a (1) 'No ASD symptom profile', (2) 'Elevated Social Affect symptom profile', (3)'Elevated Restricted/Repetitive Behaviors symptom profile' and (4)'severe ASD symptom profile'. We also identified a four-profile model for the SRS, with a (1)'No ASD symptom profile', (2)'Mild ASD symptom profile', (3)'Moderate ASD symptom profile', and (4)'Severe ASD symptom profile'. Both models showed methodological stability. IQ was lower in both severe symptom profiles. We also found differences in the distribution of syndrome groups and sex across profiles.

Conclusion: We found multiple distinct ASD symptom profiles in a population consisting of FXS, AS, TSC, and NF1 patients. Symptom profiles seem to be associated with syndrome, sex and IQ. This study endorses the importance of and need for a personalized approach in the identification and treatment of ASD difficulties in rare genetic syndromes. Future studies should aim to validate these results in a non-syndromic ASD population.

Keywords: Autistic traits, ASD, symptom profiles, genetic syndromes, children, person-centered approach

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Don't forget about me: Dementia in rare genetic neurodevelopmental disorders, a systematic review

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Rationale: While the developmental course of children with rare genetic neurodevelopmental disorders (RGNDs) is increasingly known, cognitive trajectories throughout adulthood are understudied. Early onset of decline in functioning is often seen clinically. This may be caused by dementia, which has been studied rather extensively in Down Syndrome but barely in other genetic neurodevelopmental disorders. The aim of this systematic review was to study associations between RGNDs and dementia in order to improve dementia recognition and care in this population.

Methods: A search was conducted in several databases. Search terms were related to dementia and genetic neurodevelopmental disorders in adults, the latter including generic search terms for neurodevelopmental disorders as well as an extensive list of rare genetic syndromes from the National Institute of Health. As studies on dementia were expected to be scarce, broader search terms on cognitive and adaptive decline were also included. This search yielded a total of 11,917 articles to be screened. Title, abstract and reference screening reduced this to 199 full-text articles. This led to a total inclusion of 36 articles in 17 different syndromes in 4,985 adult patients, from which data was extracted.

Results: Results will be presented on epidemiology, pathology, and clinical manifestations of dementia and cognitive decline in rare genetic neurodevelopmental disorders. Validity of diagnostic methods, strengths and limitations of the studies are reported. Qualitative and descriptive analyses were performed.

Discussion: Findings shall be discussed, providing recommendations to optimize screening and diagnosis of dementia and care for adults with neurodevelopmental disorders. A neuropsychological test battery is proposed. Converging pathways between genetic neurodevelopmental disorders and dementia are explored.

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Integrated Care for Young People with 22q.11.21 Deletion Syndrome – A Patient, Provider Initiative

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Introduction: A disease specific 22q.11 Deletion Syndrome clinic was established in Children's Health Ireland (CHI) to meet the needs of families living with this rare disease. A 'Patient and Public Involvement' ethos underpins this initiative, completed in conjunction with 22qIreland, a parent support group. Families reported significant difficulty in coordinating care for their children, and many are linked with multiple hospital sub-specialities, community based disability and mental health services. Assessment by a general paediatrician allows signposting to appropriate services. A Complex Care Coordinator and adult physician provide support related to disability related needs, mental health and transition.

Objectives

1) Patient provider Collaboration – involve users in healthcare

2) Establishing a disease specific 22q.11 Clinic

3) Improve Transition for young people with 22q11.DS

Implementation: This initiative is a partnership collaboration involving people with lived experience, their families (through 22q11 Ireland), clinicians and the health service working together to improve integration and co-ordination of services at community and hospital level.

A Consultant Paediatrician with the support of a Complex Care Coordinator leads a fortnightly, disease-specific clinic. The chairperson/ parent representative from 22qIreland also attends the clinic, and provides disease specific information and support in the waiting room. The team collaborated with an adult physician in St. James Hospital (SJH), which will be co-located with the new National Children's Hospital (opening 2025). This physician attends the adolescent clinics in CHI, and the transition pathway and process is planned. Transition clinics have commenced in SJH with the same team in CHI, to ensure continuity and reduce the gathering of medical information

Outcomes: The Complex Care Coordinator for children and adolescents living with 22q11.2 Deletion Syndrome has created an innovative healthcare model, where a single, allocated person is overseeing integrated care, with a focus on transition from paediatrics to adult services.

Parents report improved coordination of care, and less self-management of communication between services. Parents also report improved access across specialities, with same day access facilitated. Parents have support from diagnosis to adulthood, with a lifelong Model of care submitted that is transferrable to other diseases.

It is difficult to put a value on integrated care, and difficult to measure it, but families living with 22q report significant improvement in their experience of their hospital journey and navigating the complex web of specialities and services. Innovative collaborations are one of the key factors in achieving integrated care, and this project highlights the need to collaborate in new ways and with people and organisations that provide services for these families.

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Recognizing collagenopathy disorders in neuropaediatrics: a case series

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Introduction: The collagenopathies are a heterozygous group of inherited conditions which are caused by genetic defects of collagen formation. Collagen disorders affect multiple organ systems depending on the specific collagen defect including skin, musculoskeletal, vascular, and central nervous system. Due to their ubiquitous nature collagenopathies can present to many specialty clinics but can be difficult to recognize due to their individual rarity. A high level of suspicion must be present to inform further diagnostic testing to ensure optimal management of these children.

Case Series: We present a case series of four children presenting recently to our unit and seek to highlight collagenopathy disorders presenting with a variety of developmental symptoms.

Case 1: An eighteen-month-old boy with hypotonia and gross motor delay. On examination, he had several dysmorphic features notes and significant joint hypermobility. A diagnosis of vascular Ehlers-Danlos Syndrome (EDS) with a *COL3A1* pathogenic variant was confirmed on genetic testing (Collagenopathy panel).

Case 2: A two-year-old girl with gross motor delay and headaches, with joint hypermobility. She had clinical features of classical EDS which was confirmed by genetic testing demonstrating a *COL5A1* novel pathogenic variant (Collagenopathy panel).

Case 3: A five-month-old girl with a right sided hemiplegia whose genetic testing revealed a *COL4A2* pathogenic variant which led to identifying multiple family members affected with cerebral vasculopathy (targeted testing).

Case 4: A five-year old boy who attended the neurology clinic with challenging behavior (subsequently found to be due to fatigue and joint pain) with a background notable for sensorineural hearing loss and high myopia. A full clinical examination revealed joint hypermobility. Diagnostic investigations were performed appropriate to the findings and a targeted genetic diagnosis of *COL2A1* Stickler syndrome was made.

Discussion: Collagenopathy disorders can present to any general or specialty-based paediatric clinic. We present just four varying presentations and diagnoses to the neurodevelopmental and neurology clinics. Joint hypermobility is an important clue. All four cases highlight the importance of a thorough history and clinical examination to inform diagnostics and support management of the appropriate condition. While precision diagnosis is important for management and counselling, there is a major treatment gap and need, as there are no molecular-based precision therapies available for the cases described above.

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Psychiatric findings in adults with Triple X syndrome

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Aim: Research on psychiatric symptoms in women with triple X syndrome (TXS) is scarce, particularly in adults, although previous case series mentioned an increased vulnerability to psychiatric disorders. We aim to fill this gap.

Method: We will present the results of a cross-sectional study in 34 TXS women and 31 controls. The Social Responsiveness Scale – Adult version (SRS-A), the MINI International Neuropsychiatric Schedule and the Adult Behaviour Checklist (ABCL) were used to assess psychiatric symptoms. We compared the psychiatric symptoms of the TXS group to the control group. Within the TXS group, we compared the women with impairments in social functioning with women without those impairments.

Results: The results showed that women with TXS appeared more vulnerable to impairments in social functioning, psychotic disorders, and depressive and anxiety symptoms. Moreover, women with TXS more often showed suicidal thoughts and behaviour. In addition, women with TXS with impairments in social functioning had more psychiatric symptoms than women with TXS without those impairments.

Conclusion: adults with TXS show an increased vulnerability to psychiatric symptoms, especially if they have impairments in social functioning.

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Disabling Fatigue in adults with Neurofibromatosis type 1: a multidisciplinary approach

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Context: Neurofibromatosis type 1 (NF1) is a complex neurocutaneous syndrome that is caused by alterations in the RAS pathways. It is characterized by the presence of benign and cancerous tumors, scoliosis and neuropsychological problems, among others. Adults with NF1 often suffer from chronic and severe fatigue, which may intervene with daily life and even cause absenteeism from school/work. The diagnostic trajectory of fatigue is extensive and usually includes (invasive) diagnostic procedures. To prevent the personal and financial burden of (the analysis of) this disabling fatigue, it is crucial to know the causes.

Objective: To assess the prevalence of underlying organ and hormone problems in order to provide practical recommendations for the approach to fatigue in adults with NF1.

Design: Cross-sectional study. All adults with NF1 (N = 133) who visited the department of internal medicine for adults with rare genetic syndromes underwent a systematic health screening, including a medical questionnaire, structured interview, complete physical examination, biochemical measurements and, if indicated, biomedical imaging.

Main Outcome Measure: Prevalence of organ and hormone problems among NF1 adults with and without fatigue.

Results: In our cohort, 75% of NF1 adults experienced fatigue. The most frequent internal medicine disorders were high blood pressure (42%), vitamin D deficiency (28%), obesity (18%) and hypothyroidism (8%). None of the disorders differed significantly between adults with and without fatigue.

Conclusions: Organ and hormone problems are equally present in NF1 adults with and without fatigue. This suggests that the high prevalence of fatigue in NF1 adults is not explained by these somatic disorders. An alternative explanation for fatigue might be deficits in cognitive functioning and other neuropsychological processes in NF1. Based on our results and review of the literature, we provide a clinical algorithm for the multidisciplinary approach to fatigue in NF1 adults, including somatic and psychological assessment.

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Clinical study of Lamb-Shaffer Syndrome in Spain

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Introduction: Lamb-Shaffer syndrome (LAMSHF; OMIM #616803; ORPHA #313892; ORPHA #313884), described in 2012 (1), is a neurodevelopmental disorder caused by genetic alterations in heterozygosity of the SOX5 gene located on chromosome 12p 12(1,2,3,4), which encodes a transcription factor critical in neurogenesis. It is an ultra-rare disease (prevalence <1/1000000). There are currently 17 patients diagnosed in Spain. LAMSHF is characterized by neurodevelopmental disorder and intellectual disability, language impairment, visual impairment, Autism Spectrum Disorders features, digestive and feeding disorders (5).

Objective: To study the clinical, radiological and genetic characteristics of LAMSHF patients in Spain. Also, to share the knowledge of LAMSHF with the medical and scientific community.

Methodology: We retrospectively collected clinical, genetic, phenotypic and radiological data from 12 patients diagnosed of LAMSHF. The clinical data included 36 variables related to neurodevelopment and different systems.

Results: The group included 12 patients with a mean age of 12 years old (range: 2-32). 100% of the patients presented neurodevelopmental disorder (onset of free walking between 18 months - 3 years, first words between 15 months - 6 years). 100% present neurological, language and behavioral alterations. 91.6% present visual disturbances and 50% digestive and/or feeding disorders.

Genetic diagnosis was obtained at an average age of 9.4 years old. Most of them were de novo mutations. We recorded Magnetic Resonance Imaging of the brain of 7 patients, 4 of them showing slimming of the optic nerves as the only finding.

Conclusions: LAMSHF should be included in the differential diagnosis of neurodevelopmental disorders. Early genetic diagnosis would allow the initiation of early care programs to promote clinical improvement. We recommend that the study of the SOX5 gene should be included in the neurodevelopmental and intellectual disability.

There is great discordance between clinical manifestations and imaging tests.

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Analysis of neurodevelopmental, behavioral and social status of Polish adult population of Cornelia de Lange Syndrome

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Cornelia de Lange Syndrome is a neurodevelopmental disorder, characterized by the microsomia and proportional microcephaly, distinctive dysmorphic features, congenital malformations, including limb deformities, hypoacusis and gastrointestinal complications. The main part of the clinical picture is intellectual disability, lack of normal speech and some of behavioral disorders.

It is caused by various types of mutations in genes involved in the chromatin regulation, especially the cohesion complex (*NIPBL, SMC1 ,SMC3, RAD 21, HDAC8, BRD4).*

As general CdLS phenotype has already been widely described, we would like to focus on abnormalities presented by adult population, with an attempt to establish genotype-phenotype correlation. Out of 208 patients-members of Polish CdLS Association, 49 are adults, the oldest one has 44 years, 4 of them died in the follow-up period of 20 years (2001-2022) as adults. Many years of clinical observations, as well as phone call questionnaire and medical documentation review were a source of below described CdLS adults data. Among adult patients 45 had *NIBPL* gene mutations, including 2 rearrangements, 2 had *SMC1A* and 1 had *RAD21* and 1- *HDAC8* gene mutations. Truncating/deletions/missense mutations were more common among patients with severe phenotype in comparison with missense/in frame/splice site mutations in mild one. Near all had neurological abnormalities including 8 patients with well controlled epilepsy. Regarding speech development, 11 patients were able to speak words, 16 in sentences, remaining 22 communicated only with gestures. The main behavioral disorders presented among adults were: anxiety, autism, aggression and stereotypes. Also sleep disorders were stated by majority of CdLS adults. Patients declared to spent most of their time at school/job (10 pts), day care centers (18) or had home education (10). Patients with the non NIPBL mutations demonstrated milder phenotype , all of were able to speak with no autistic behavioral features. Regarding recent pandemic issues – almost all adults were vaccinated, 10 were diagnosed with COVID, out of whom 6 had mild course, 3 developed complications (pneumonia, invasive ventilation) and 1 died.

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Case report of Potocki-Lupski Syndrome diagnosis in adulthood

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Background: There are a lot of adult patients with intellectual disability without genetic diagnosis due to genetic testing availability limitations in the past. These patients circulate in different fields of internal medicine. Our aim is to show importance of correct genetic diagnosis even for adult patient.

Case report: 28 years old female was referred to clinical geneticist by the consulting cardiologist due to heart arrhythmia. The patient was full term baby, but delivery was complicated, and she was born in hypoxia. The psychomotor development was delayed: the patient started to sit at 12 month of age, to walk – at 20 month of age. There were feeding difficulties, swallowing problems, regurgitation, and failure to thrive. Severe language development was determined – she started to speak at the age of 4 years old. Due to learning disability, she had special education plan and finished 10 grades of secondary school. Afterwards she continued with profession education, later on she got married. The patient had the diagnosis of mild intellectual disability. She has obesity, hypothyroidism, and menstrual cycle dysregulation. She is on regular observation by endocrinologist and cardiologist.

During the clinical visit, we noticed soft dysmorphic features: inverted triangle shape, down slanting palpebral fissures, and relatively small jaw. Clinodactyly of 3rd 4th and 5th toe also was documented. Her height was 167 cm, weight 100 kg, BMI 35,9 (2nd grade obesity). There had also striae and hirsutism.

After evaluation the patient's phenotype, anamnesis, and current symptoms the decision to perform molecular karyotyping was made.

Result: Whole Genome NGS-based Large Copy Number Variation Analysis (Centogene, German) was performed and a heterozygous pathogenic 3519 kb - large gain at 17p11.2 cytoband was identified.

The genetic diagnosis of the Potocki-Lupski syndrome was confirmed. The condition is characterized by infantile hypotonia, failure to thrive, cardiovascular malformations, developmental delay, intellectual disability, and behavior abnormalities, the latter of which can include autism spectrum disorder. The critical genes related to this syndrome are mainly RAI1, SREBF1, SHMT1, DRG2 and LLGL1.

Conclusions: Despite that patient was referred due to suspicion of inherited isolated arrhythmia; it was decided to pursue molecular karyotyping to rule out a possible syndromic cardiovascular case. It is important to get detailed childhood anamnesis in adult patient as it can lead to better diagnostic procedures. The diagnosis of Potocki-Lupski syndrome is consistent with previous and current patient symptoms. The managent plan and propper genetic councelling was made.

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Improving detection of rare overgrowth syndromes among patients referred to the endocrinology ward for treatment of acromegaly

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Background: A common request at an endocrine outpatient clinic is to rule out acromegaly in a patient with acromegaloid features. It is important to do so, since the excessive excretion of growth hormone can result in various serious comorbidities. But when growth hormone-IGF-1 axis abnormalities are excluded, the physician faces a diagnostic dilemma. Here we provide a systematic approach to these patients.

Methods: We present a case series of patients visiting our outpatient clinic for 'acromegaly', from presentation to diagnosis. We describe the diagnostic challenges and illustrate the added value of multidisciplinary treatment, initiated once patients were diagnosed with overgrowth syndromes. Additionally, we conducted a systematic review of the literature on overgrowth syndromes.

Results: The patients presented with acromegaloid characteristics without growth hormone/IGF-1 axis abnormalities. Endocrine and genetic work-up ruled out acromegaly and revealed mutations in *CHD8*. Neuropsychological assessment revealed a mild intellectual disability in one of the patients, which had remained unnoticed for years due to relatively strong verbal performance. To initiate ID support, the patient was referred to the physician for intellectual disabilities.

Based on our own expertise in combination with the existing literature, we made an algorithm to improve diagnostics and management of adults with overgrowth syndromes. Due to their physical and neuropsychological problems associated with some overgrowth syndromes, multidisciplinary care is often necessary.

Conclusions: When a patient presents with acromegalic features in the presence of normal IGF-1, the diagnosis of overgrowth syndromes should be considered as underlying condition. As overgrowth syndromes may be associated with neurodevelopmental delay, we recommend to screen for mild ID and refer patient for multidisciplinary management to prevent the complications of undiagnosed ID.

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Healthcare needs of people with NDD PROM4RARE: Giving a voice to individuals with a rare genetic disorder associated with intellectual disability

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Background: In order to improve quality of care for individuals with a rare genetic disorder associated with intellectual disability (GD-ID), it is essential to measure patient reported outcomes (PROs). PROs represent patient perspective on their health status and can be measured with patient reported outcome measures (PROMs). PROMs can be used in the consultation room to monitor and discuss symptoms and physical and psychosocial functioning. Unfortunately, the use of PROMs in clinical care for individuals with GD-ID is scarce, due to the unsuitable and time-consuming questionnaires.

Objective: The objectives of this study are to (1) develop a core outcome set (COS) of PROs (CoPROs) for GD-ID, (2) select suitable generic PROMs with the best psychometric properties and add specific questions for GD-ID, (3) validate the core PROM set (CoPROMs) for GD-ID, and (4) implement the CoPROMs in daily clinical care for individuals with GD-ID.

Study design: We will use a mixed method design; (1) CoPROs: Identifying common PROs measured in clinical trials (review) and perform a qualitative study on the relevant PROs for individuals with GD-ID and their caregivers (focus groups). Eventually, reaching consensus on the most important PROs for GD-ID (Delphi method). (2) CoPROMs: Identifying and selecting PROMs, which measure the CoPROs (review). (3) Subsequently, validate the CoPROMs for the GD-ID population. (4) Implementation of CoPROMs at the Emma Children's Hospital, Amsterdam UMC and at 's Heerenloo, a large care organization for individuals with ID.

Prospections: With the identification of relevant PROs, the development of a CoPROMs, and implementation of the CoPROMs, we hope to maximize personalized care and science for the complex and vulnerable patient population with GD-ID.

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Parkinsonism in individuals with genetic neurodevelopmental disorders: a systemic review

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Introduction: Parkinsonism has been increasingly reported in individuals with genetic neurodevelopmental disorders (GNDs). We aimed to provide a comprehensive overview of reports on parkinsonism in GNDs and summarize findings related to genetic diagnosis, clinical features and proposed disease mechanisms in addition to implications for clinical practice and future research.

Methods: We conducted a systematic literature review, and searched PubMed and Embase on June 15, 2021. General search terms for GNDs, and a list of neurodevelopmental disorders as per the Human Phenotype Ontology, were combined with terms for parkinsonism. Study characteristics and descriptive data on GNDs and parkinsonism were extracted from the included articles. The protocol was registered in PROSPERO (CRD42020191035).

Results: Our search yielded 208 reports, describing 69 different GNDs in 422 patients. The five most reported GNDs were: 22q11.2 deletion syndrome, beta-propeller protein-associated neurodegeneration, Down syndrome, cerebrotendinous xanthomatosis, and Rett syndrome. Median age of motor onset was 26 years. Response to antiparkinsonian medication, and results of dopaminergic imaging were often supportive of Parkinson's disease. Neuropathology results showed neuronal loss in the majority of cases reported, indicative of an overlap in neurodevelopmental and neurodegenerative processes. Proposed disease mechanisms included aberrant mitochondrial function, autophagic-lysosomal system, neurotransmitter metabolism, endosomal trafficking and the ubiquitin-proteasome system (Figure 1).

Conclusions: Parkinsonism has been reported in many GNDs. The presence of parkinsonism in a neurodevelopmental disorder may prompt physicians to consider genetic testing, facilitating precision medicine.

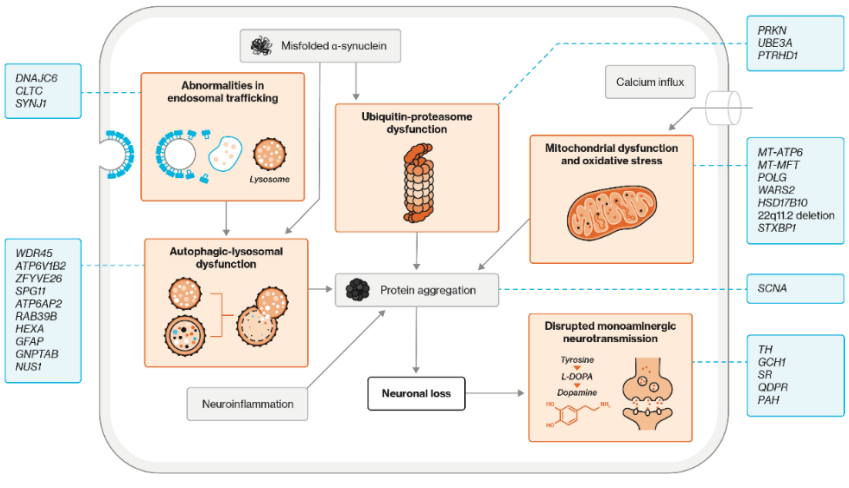

Figure 2. Mechanisms underlying parkinsonism in genetic neurodevelopmental disorders.
Representation of a neuron depicting mechanisms that are thought to be involved in the pathogenesis of parkinsonism in genetic neurodevelopmental disorders.

Blue boxes indicate examples of associated genetic mutations.

Orange boxes indicate pathophysiological mechanisms that have been reported most in genetic neurodevelopmental disorders.

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Theme 4 – Mechanisms of diseases, model systems & translational pre-clinical work

Pontocerebellar hypoplasia genetic diagnosis: experience of our reference center

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Pontocerebellar hypoplasias (PCH) are congenital disorders characterized by hypoplasia or early atrophy of the cerebellum and brainstem, leading to very limited motor and cognitive development. Classical PCH includes 17 subtypes listed in the OMIM database, and are considered neurodegenerative disorders, with frequent involvement of RNA metabolism or function. However, some of those subtypes do not have a degenerative course (TBC1D23 for example), and other genes are responsible for brainstem and cerebellum hypoplasia or atrophy (CASK, SPTAN1, etc..) with non-progressive or degenerative evolution. Moreover, a large proportion of patients remain undiagnosed.

Our reference center is involved in the care and diagnosis of congenital cerebellar disorders. Between 2011 and 2022, 266 PCH patients (children and fetuses) were referred to our center and investigated for genetic diagnosis. Patients with multiple congenital anomalies and with predominant brainstem hypoplasia or malformation were excluded. In two patients, the posterior fossa anomalies were linked to an ischemo-hemorrhagic mechanism. The first round of genetic analysis included ACPA, Sanger sequencing in the first years, then NGS targeted panel (the last one including 29 PCH genes). We were able to reach a diagnosis in 159 patients using this first approach. Two patients had a chromosomal anomaly (chr 5). In patients with a monogenic diagnosis (157), the main genes were *CASK* (n=55) and *TSEN54* (n=45). Our panel allowed the detection of *CASK* exonic deletions, one of them being a mosaic deletion in a male fetus. Variants were identified in *EXOSC3, EXOSC9, MINPP1, COASY, TOE1, VLDLR, TSEN2, GRID2, MED17, SEPSECS, CLP1, INPP4A, TBC1D23, RARS2, and CHMP1A*. Some patients had a tubulinopathy that could be misdiagnosed in PCH in some cases, particularly fetal cases.

In patients without a genetic diagnosis after the panel analysis, we performed trio exome sequencing when parental DNA was available. We identified pathogenic variants in genes involved in DNA reparation (*ERCC1, ERCC2, ERCC5*), in *PRDM13*, and *VPS4A*. Interestingly, we also identified pathogenic variants in genes previously involved in intellectual deficiency and careful analysis of the literature showed that some published patients have pontocerebellar anomalies (*DYRK1A, PPP2R1A, EPG5, KPNA3*,..). For all of these patients, MRI was reviewed and we confirmed the presence of a small brainstem and cerebellum. The analysis is still ongoing and we are also reviewing the files and MRI of the remaining patients.

In conclusion, besides the 17 PCH subtypes, some other diagnoses may be identified in patients harboring a small brainstem and cerebellum. The distinction between a neurodegenerative or non-progressive course is not always obvious, particularly in fetuses and young children. We were able to reach a 60% diagnosis rate using a panel including 29 PCH genes. We recommend this approach as the first round after a careful clinical and MRI assessment.

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DNA Methylation episignature in Gabriele-de Vries Syndrome

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PURPOSE: Gabriele-de Vries syndrome (GADEVS) is a rare genetic disorder characterized by developmental delay, and/or intellectual disability, hypotonia, feeding difficulties and distinct facial features. In order to refine the phenotype and to better understand the molecular basis of the syndrome, we analyzed the clinical data and performed genome-wide DNA methylation analysis of a series of individuals carrying an YY1 variant.

METHODS: Clinical data were collected for 13 individuals not yet reported through an international call for collaboration. DNA was collected for 11 of these individuals and 2 individuals previously reported in an attempt to delineate a specific DNA methylation signature in GADEVS.

RESULTS: Phenotype in most individuals overlapped with the previously described features. We also describe one individual with atypical phenotype, heterozygous for a missense variant in a domain usually not involved in individuals with YY1 pathogenic missense variations. We described a specific peripheral blood DNA methylation profile associated with YY1 variants.

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CONCLUSION: We report a distinct DNA methylation episignature in GADEVS. We expand the clinical profile of GADEVS to include thin/sparse hair and cryptorchidism. We highlight the utility of DNA methylation episignature analysis for classification of variants of unknown clinical significance.

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Understanding the effect of ANKRD11 haploinsufficiency on early brain development

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Heterozygous loss-of-function variants in *ANKRD11* cause KBG syndrome (MIM# 148050), a neurodevelopmental disorder. The clinical features of KBG syndrome include mild intellectual disability and/or developmental delay, macrodontia of the upper central permanent incisors, short stature, skeletal and craniofacial anomalies, and behavioral disturbances. *ANKRD11* is among the top 3 mutated genes in next generation sequencing studies in neurodevelopmental disorder cohorts. Despite the relatively high prevalence, little is known about the role of ANKRD11 in human brain development, which hampers the development of syndrome-tailored interventions. Hence, we aim to study the consequences of ANKRD11 haploinsufficiency on early human brain development using unguided neural organoids.

ANKRD11 functions as a transcriptional repressor by binding chromatin modifying enzymes. Previous studies demonstrated that knockdown of *Ankrd11* results in reduced proliferation and neurogenesis *in vitro* and aberrant distribution of radial precursor-progeny, delayed radial migration of cortical neurons, reduced dendrite outgrowth and branching, and abnormal dendritic spine morphology *in vivo*. Based on this, we expect an important role of ANKRD11 during early human brain development, which can be further studied using human neural organoids. We acquired KBG syndrome patient-derived induced pluripotent stem cell (iPSC) lines. We will compare the tissue architecture in neural organoids derived from these lines with healthy controls and an *ANKRD11* haploinsufficient isogenic line, focusing on the temporal and spatial distribution of different cell populations, cell proliferation and differentiation.

In a pilot experiment, we compared the bulk transcriptome of iPSCs derived from two KBG syndrome patients to that of two healthy control lines. We found a clear difference between patients and controls. Specifically, gene ontology analysis showed an overrepresentation for genes with neuronal functions in patient iPSCs. We hypothesize that differences will be even more pronounced after differentiation into neural tissue. Therefore, we will perform single cell RNA sequencing on unguided neural organoids at different time points to study the effect of ANKRD11 haploinsufficiency on the transcriptome. This will generate further ideas on the molecular mechanism underlying aberrant early neurodevelopment in KBG syndrome patients.

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7-TESLA IN-VIVO 1H-Magnetic Resonance Spectroscopy of glutamate & GABA in 22Q11.2 copy number variants

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Introduction: 22q11.2 copy number variants (22q11.2 CNVs) are genetic disorders caused by a microdeletion (22q11.2DEL) or microduplication (22q11.2DUP) at chromosome 22. 22q11.2DEL individuals are at increased risk of developing psychotic disorders and impaired cognitive functioning, while it has been suggested that 22q11.2DUP individuals may have a reduced risk of developing psychotic disorders[1]. Psychosis and cognitive impairments have been linked with glutamatergic and GABA-ergic dysregulation[2]. Here, we aimed to investigate alterations in glutamate and GABA concentrations in the ACC in patients with 22q11.2 CNVs.

Methods: Eight 22q11.2DEL patients (mean age = 36.75; M/F = 3/5; mean IQ = 81.63) and 3 22q11.2 duplication syndrome (22q11.2DUP) patients (mean age = 32.67; M/F = 2/1; mean IQ = 100.67) without a history of psychiatric illness and 14 matched healthy controls (mean age = 30.71; M/F = 7/7; mean IQ = 109.36) were enrolled in this study. We collected glutamate and GABA concentrations in the ACC using 7-Tesla magnetic resonance spectroscopy (^{1}H-MRS).

Results: We did not find significant differences in glutamate concentrations between groups (F *(2,21)* = 0.657; p = 0.528; η^2 = 0.059). In addition, we did not find significant differences in GABA concentrations between groups (F (2,13) = 0.592; p = 0.567; η^2 = 0.083).

Discussion and conclusion: These findings are in line with previous studies in 22q11.2DEL patients, showing no glutamatergic alterations in this population compared to controls[3,4]. Given that our sample size was relatively small, resulting in decreased power to detect statistically significant differences, we cannot exclude the possibility of an altered glutamate/GABA balance in 22q11.2 CNVs. However, data collection for this study is still ongoing. More and larger studies are required to replicate these findings in 22q11.2 CNVs.

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Theme 5 – Ethical, legal and Psycho-social aspects

Parents of a child with a rare neurological as stakeholders of his social and education process- a case study analysis

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The presented case study is an example of the functioning of a child with a rare neurological disease resulting with complex cognitive and motor disabilities and therefore a set of unique educational and social needs. The discussed case study is based on the successful implementation of the pedagogical experiment in Polish primary school. The pedagogical experiment is defined in the Polish legal system as a *modification of existing or implementation of new activities in the education process, using innovative program, organizational, methodological or educational solutions, within which the conditions, organization of educational activities or the scope of the teaching content are modified.* The experiment combines the features of the individual learning model with planned peer integration activities and the implementation of the general core curriculum with holistic learning, as well as attempts to build social inclusion of child with special care needs. Moreover, due to lack of verbal communication abilities combined with severely impaired motor functions of the child the experiment also tries to accommodate the need of building individual alternative and augmentative communication (AAC) system coherent within the whole educational and therapeutic team.

Authors also describe efforts undertaken by the parents of the child which arise out of the need generated by insufficient systemic support as well as the complexity of the educational, health and social needs of the child. The authors as well review the available research on the education of a child with a rare disease in terms of systemic possibilities and continuum of parental engagement as stakeholders in adjusting the education process to the child's abilities and needs.

Furthermore, the case study analysis underlines the importance of institutional readiness for building organizational culture for diversity, equity and inclusion of children with health and educational special needs in the regular school system.

Summary of the author's considerations highlights the specific situation of children with a rare disease implying the need of creating alternative educational paths by their parents, implementation of solutions adapted to the individual characteristics of the child, which are undoubtedly contributing towards building a more flexible education system for children with special educational, social and health needs. The importance of actions taken in the described case concerns both issues related to the normalization of the social environment and integration as well as social inclusion, but also to the role of parents of children with rare diseases, as stakeholders, in the process of supporting the development of their children.

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Contributing factors to parental stress in neurodevelopmental disorders; An international survey among 587 PMS families worldwide

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Background*:* Parents of children with Neurodevelopmental Disorders (NDD's) and Intellectual Disability (ID) experience higher levels of stress compared to parents of typically developing children[1,3,7]. Contributing factors differ according to the specific behavioral phenotype of the NDD[3]. Phelan-McDermid syndrome (PMS) is a specific NDD, caused by deletion or mutation of the SHANK3 gene, with a behavioral phenotype of ID and Autism Spectrum Disorder (ASD)[6,8]. Chronic stress negatively impacts on different levels: micro-level for health and well-being of the parent, meso-level for the child in need of co-regulation, and macro-level on parental participation in society[2]. Therefore, informing appropriate NDD specific interventions is important. We studied parental stress and contributing factors in parents of children with PMS worldwide to guide interventions in this NDD based on the behavioral phenotype of PMS.

Method: Parents of 587 children with PMS were recruited through patient organizations worldwide on request of the European PMS guideline consortium. Parents completed a general questionnaire and the Genetic Syndromes Stressor Scale (GSSS) measuring parental stressors on a 0-3 points Likert scale ranging from 0 (not at all stressful) to 3 (extremely stressful). The GSSS is reliable and valid[3].

Results: Preliminary results showed elevated general and specific contributing factors to parental stress in this NDD. The results showed differences for individual (genetic, behavioral) and external factors (access to care, level of care). Contributing factors are constant vigilance of the child's health status, arranging suitable care, and worry about lack of specialist services in adulthood. A very strong contributing factor in PMS, the high level of vigilance to monitor the child's health status, is related to limited expressive communication skills in PMS. Stress about specialist services in adulthood is related to external factors but also to the specific development of psychiatric problems in adolescence and adulthood in the behavioral phenotype in PMS. The results will be presented in more detail at the meeting.

Conclusions: The level of parental stress is high in parents with a child with a specific NDD such as PMS and the diagnosis of the genetic syndrome itself has a limited effect on stress. Specific factors related to the behavioral phenotype are contributing to parental stress. Interventions for PMS were developed in cooperation with parents and based on the specific contributing factors. For instance a structured surveillance scheme to support health monitoring and early detection of health issues. The example of a NDD like PMS showed that psychosocial interventions based on the specific behavioral phenotype of the NDD are of importance in day to day care. Therefore information about the behavioral phenotype in NDD's is needed to guide treatment in general and interventions on parental stress. Not only the parents, but the child and society may likely also benefit from specific psychosocial interventions.

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Neurodevelopmental disorders in Wiedemann-Steiner syndrome

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Background: Wiedemann-Steiner syndrome (WSS) is a rare genetic diagnose located on chromosome 11q23.3. The critical gene is the KMT2A-gene. Typically symptoms is developmental delay, characteristic facial features, short stature and intellectual disability. The clinical characteristics vary within the group. ID severity is described mainly as mild and moderate, but there is also someone with severe ID. Neurodevelopmental disorders in WSS has been scarcely described.

Method: This study included parents of 14 children, adolescents and adults with WSS. We used standardized questionnaires such as Social Communication Questionnaire, Sensory Responsiveness Scale, Developmental Behavior Checklist (parent) and Vineland Adaptive Behavior Scales II as measures.

Results: Only Vineland and SRS are scored thus far. On Vineland the persons with WSS had a mean of 65 (SD 14). The lowest score was 43, the highest 101. On SRS the mean Total T-score was 78.55 (SD 11.56) The lowest score was 60, the highest 97.

Conclusions: With limited data at this time, no conclusion will be drawn, but will be presented at the workshop. But it already seems like the SRS scores are in the level of some deficits in social interaction for everyone in this study. The mean on SRS is above 76 which is the threshold indicating high symptomatology.
Even though this is a small sample, some beginning description of neurodevelopmental disorders in WSS will most likely be useful both for researchers and clinicians.

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Family centered approach – ICF based partnership between families and professionals

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Objectives: The objective of the presentation is to present how a family centred approach has been introduced, practised and what it has resulted in.

Target audience: Educators, psychologists, physicians, speech, language and developmental therapists, occupational therapists, physiotherapists, multi-disciplinary teams, Parents.

Summary: For many years we have been taught that disability is mainly deficits and dysfunctions that we should work on as specialists. This had a huge impact on how we used to build relationships with families. For most of the time, we were service providers who set goals, made decisions about the implementation of support, and eventually assigned tasks to parents. The ICF and the UN Convention on the Rights of Persons with Disabilities have completely redefined disability and made us start working with people with disabilities and their families in a completely different way than before. First of all, ICF has redirected our attention to resources instead of deficits. This means that the main aim of our work is not so much to "heal" as to support development. Secondly, it has showed us that health and well-being are not just body functions and structures. It is also participation, activities, personal factors and environmental factors, which means that we need to work in transdisciplinary teams and that a family has to be a part of this team.

Building partnerships with families is not an easy task however. We need to reorganize our work, introduce rules for partnership based on communication with parents, share goals, and above all, change attitudes. But it is worth the effort as the effects are felt not only for children and young people with disabilities, their families, but also for us, professionals.

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Theme 6 – Genes and pathways

The Neurodevelopmental Spectrum of Synaptic Vesicle Cyling Disorders

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Objectives: Advances in genomic technologies have enabled identification of many new genetic causes of neurodevelopmental disorders (NDDs), providing new opportunities for improved support and better outcomes for patients and their families. To fulfil this promise, next generation strategies are required for post-diagnostic research. One strategy is to investigate networks of NDD-associated genes, defined by molecular and cellular functions. Synaptic vesicle cycling (SVC) is one functional gene network in which rare, high penetrance variants are known to cause a spectrum of NDDs. Understanding the phenotypic spectrum and convergent mechanisms of SVC disorders could improve diagnostic yield, improve prognostication, and improve care.

Methods: We systematically describe neurodevelopmental phenotypes across 80 individuals with SVC disorders (14 different single gene diagnoses, including SYT1, TRIO, STXBP1 and DNM1) and compare these to individuals with other monogenic NDDs. Data has been collected online via quantitative questionnaire measures previously validated in populations with NDDs, structured medical history questionnaire for parents / carers, and clinical summaries.

Results: Individuals within the SVC group were more than twice as likely to suffer from movement disorders and epilepsies compared to the non-SVC group. We observed a wide range of severity across all behavioural measures within both groups. The SVC group presented with a higher prevalence of severe intellectual disability and visual impairment. We found that the SVC group was not at higher risk of experiencing social-emotional or behavioural difficulties. However, we observed relative preservation of social motivation amongst SVC individuals. The presence of movement disorders, but not epilepsy, predicted poorer adaptive functioning in the SVC group. SVC individuals with movement disorders and missense variants showed more severe global adaptive impairments than individuals with movement disorders and protein-truncating variants.

Conclusions: We have characterised the range of neurological and behavioural characteristics across the SVC disorders network. Our findings provide early evidence for predictors of variation in behavioural development within the SVC network which may help to improve clinical prognostication and improve personalised support for patients and families. Our next steps are to investigate underlying mechanisms via electrophysiological studies in patients, and cellular physiology studies in experimental models.

Acknowledgements: Thank you to all families who have taken part in this study, and clinical teams who have facilitated recruitment to the study. Research funded by UKRI / MRC, and GOSH Charity.

A novel FZR1 variant causing developmental and epileptic encephalopathy

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Heterozygous loss-of-function FZR1 variants have been recently linked to developmental epileptic encephalopathies with a broad phenotypic spectrum. The first reported patient carrying a de novo FZR1 c.559G>A, p.(Asp187Gly) missense variant presented with neonatal onset multifocal seizure and severe developmental delay with microcephaly. The same de novo FZR1 missense variant has been identified in a patient with childhood onset generalised epilepsy, moderate developmental problems and normal head circumference. Two other patients carrying de novo FZR1 c.999C>G, p.(N333K) missense variant showed a similar clinical course of developmental epileptic encephalopathy with delayed myelination on brain MRI. Myoclonic atonic epilepsy has been diagnosed in two of the three childhood onset epilepsy patients and all 3 patients had mild gait ataxia.

FZR1 has been implicated in neurodevelopment by regulating the cell cycle and by having prominent function in post-mitotic cells in the central nervous system. Both reported variants affect the same FZR1 domain, result in decreased protein stability and lead to functional protein deficits in Drosophila assay.

We report a novel de novo FZR1 c.1333C>G, p.(Arg445Gly) missense variant identified by WES trio sequencing in a 3-year-old girl. This variant is absent from the gnomAD database and affects a residue within the same WD40 domain as the previously reported variants. Our patient had neonatal hypotonia, infantile spasms and delayed motor milestones. Clinical assessment at 3 years detected severe developmental delay, central visual impairment, microcephaly and therapy resistant generalised epilepsy with myoclonic seizures. Brain MRI revealed delayed myelination and frontal lobe volume reduction.

We consider that this patient, based on the overlapping phenotype and genetic findings, extends the cohort of FZR1-encephalopathy and broadens the phenotypic spectrum.

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New NDD candidate genes discovered and followed-up through the Norwegian ERN-ITHACA network

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The Norwegian ERN-ITHACA network is a group of clinicians, laboratory scientists and researchers involved in the care and genetic investigation of individuals with rare or undiagnosed neurodevelopmental disorders (NDD) located in 5 genetic centres across the country. We present three singleton cases with novel NDD candidate genes in an effort to match our findings:

***UBE2O de novo* C-terminus alteration case**: A *de novo* frameshift variant p.(Asn1140AlafsTer49) was found in the last exon of *UBE2O* (MIM*617649) in a 14-years-old girl with mild ID including poor language function, epilepsy (onset at 2 years) and gait ataxia. A brain MRI was normal. UBE2O is a large multi-domain, hybrid E2/E3 ubiquitin ligase with high brain expression, low LoF and missense tolerance, and a proposed role in the elimination of misfolded proteins. The variant predicts a replacement of the C-terminal 152 amino acids with 49 other amino acids. In vitro functional studies in transfected HEK293FT cells indicated that the variant leads to significantly reduced UBE2O protein level (26% of wild type level), indicating protein instability of the variant. Ongoing studies investigate the ubiquitination activity of the variant protein.

***HEATR6* recessive predicted complete LoF case**: Compound heterozygosity for two nonsense variants p.(Arg655Ter) and p.(Arg973Ter) in *HEATR6* (NM_022070) was discovered in a 17-years-old girl with mild ID, corpus callosum hypoplasia, variable corneal thickness, brachytelephalangy with nail dysplasia and hirsutism. *HEATR6* is a generally expressed gene of unknown function containing an armadillo/beta-catenin-like repeat. Based on gnomAD data, similar biallelic LoF cases should occur in around $1:10^6$ births, but our variant/case has not been matched in a range of variant databases including Genomics England.

***MAF1* recessive predicted complete LoF case**: Homozygosity for a nonsense variant p.(Trp184Ter) in exon 6 (of 8) of *MAF1* (MIM*610210) was found in a boy born SGA with hypotonia, cutis marmorata, mild facial dysmorphism, microcephaly, 2-3 toe syndactyly and cryptorchidism. By 1 year of age he had failure to thrive (weight -2,4 SDS), microcephaly (-4,5 SDS) and has motor delay. Exon 6 is present in all *MAF1* transcripts. Parents are first cousins and variant segregation analysis in his four siblings did not reveal homozygosity (random finding likelihood 0.316). MAF1 is an inhibitor of RNA polymerase-III mediated transcription, important for metabolic downregulation in response to cellular stress in e.g. yeast and mice. In mice, *Maf1* is also a regulator of bone mass, and total body X-ray of the boy revealed gracile bones. MAF1 has low LoF tolerance in gnomAD (pLI 0.95, o/e 0.07), and based on gnomAD data the likelihood for compound heterozygosity or homozygosity for LoF variants in an outbred population is very low, around 3.1×10^{-8}.

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LIG4Syndrome: phenotypic variability in a consanguineous family

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DNA ligase IV (LIG4) syndrome is an ultra-rare autosomal recessive disorder characterized by a wide range of clinical features such as microcephaly, growth retardation, developmental delay, dysmorphic facial features, combined immunodeficiency, and malignancy predisposition. LIG4 syndrome is caused by mutations in DNA ligase IV, a component involved in the repair of DNA double-strand breaks (DSBs) via the non-homologous end-joining (NHEJ) pathway. We present a family of four sisters born to a consanguineous couple: a healthy one in her late fifties and the other three with neurodevelopmental delay and growth retardation. Two of them have already died, one with type 2 diabetes at around 55 years old due to acute pneumothorax, and the other one before completing 5 years old for unknown reasons. The only living affected sister presented to our consultation at 51 years old with severe cognitive impairment, short stature, type 2 diabetes, macrocytic anaemia, thrombocytopenia, and strabismus. On physical examination, we noticed microcephaly, beak-like nose, palpebral ptosis, malar hypoplasia, elongated fingers, and bilateral valgus halluces. Previous skeletal radiography, EKG, and echocardiogram were normal. We decided to perform clinical exome sequencing who identified an apparent homozygous nonsense LIG4 variant (previously reported in the literature). Even though we are not able to carry out segregation studies on the deceased parents and affected sisters, this report highlights the phenotypic variability of an ultra-rare syndrome.

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A rare case of 18q12.1q21.1 Deletion Syndrome

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Chromosome 18q deletion syndrome occurs in 1 in 40,000 live births. Terminal deletion (18q21.1-qter) is among the relatively common cytogenetic abnormalities, while proximal interstitial deletions (18q11.2-18q21.1) are rare and have recently been recognized as a new clinical entity. Few cases have been reported in the literature. Here, we present a rare case of del(18)(q11.2q21.1) with characteristic facial anomalies, developmental delay and obesity. 3 years 9 months old girl referred to Pediatric Genetics department because of developmental delay (DD), delay in neuromotor steps and speech retardation. At 22 months old, she was walking and could not speak sentences and had no history of seizures. She was born as G3P3Y3 from a 37-year-old healthy mother with a 35-week cesarean section and weighing 3250 g. She was followed up in the intensive care unit for 11 days due to respiratory distress. Pregnancy and family history were negative. On physical examination, her body weight, height and head circumference was 97p, 50-75p, and 97p respectively. Dysmorphic features include wide forehead, low and large ears, thick eyebrows, bilateral epicanthus, ptosis, strabismus, hypertelorism, downward slanting palpebral fissures, wide nasal bridge, small nose, anteverted nostrils, long philtrum, thin upper lip, full cheek, high palate, micrognathia, simian line on the left hand, bilateral clinodactyly. Her friendly personality was remarkable. Systemic examination was normal. No abnormality was found in the internal organ scan. Chromosome analysis with GTG banding method was reported as 46,XX, del(18)(q12.2q21.1)(Figure 1). A pathogenic *de novo* deletion of 13.7 Mb was detected in the 18q12.1q21.1 region (including 75 genes) in the chromosomal microarray. The operation was planned by the ophthalmology department due to ptosis. Parental karyotype and microarray analysis results were reported as normal. Chromosome 18q interstitial deletion syndrome (18q11.2-q21.1) is rarely seen and less common than distal region deletions. Short stature, behavioral problems (aggression, attention deficit, hyperactivity), autism, speech delay, cleft palate, cardiac anomalies constitute the common clinical features of microdeletion. Dysmorphic facial features may be descriptive (Figure 2). Deletions containing the *GATA6* gene in the region are held responsible for cardiac malformations. They have a tendency to obesity. It may be accompanied by epilepsy. Severe malformations in internal organs are not expected. In a study evaluating data from 29 patients, DD/intellectual disability (ID) was 82%, behavioral problems were 30%, and conotruncal heart defects were 15% among the clinical findings of 18q11-q12 deletions. The critical region for moderate to severe DD/ID was considered to be 38.8–43.5 Mb (Figure 3). The *SETBP1* gene located in the region is thought to be responsible for expressive language retardation. In addition to the findings consistent with the literature, the friendly personality of our case may also be an additional clinical finding of the deletion. Del(18(q11.2q21.1) syndrome should be kept in mind in the presence of minor facial anomalies, psychomotor retardation, obesity and epilepsy.

Figure 1. 18q proximal interstitial region deletion in the karyotype analysis of the case.

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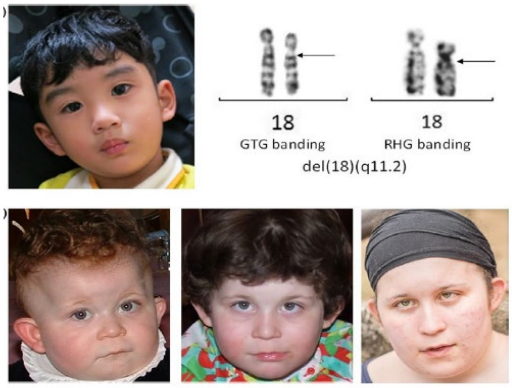

Figure 2. Some cases reported in the literature.

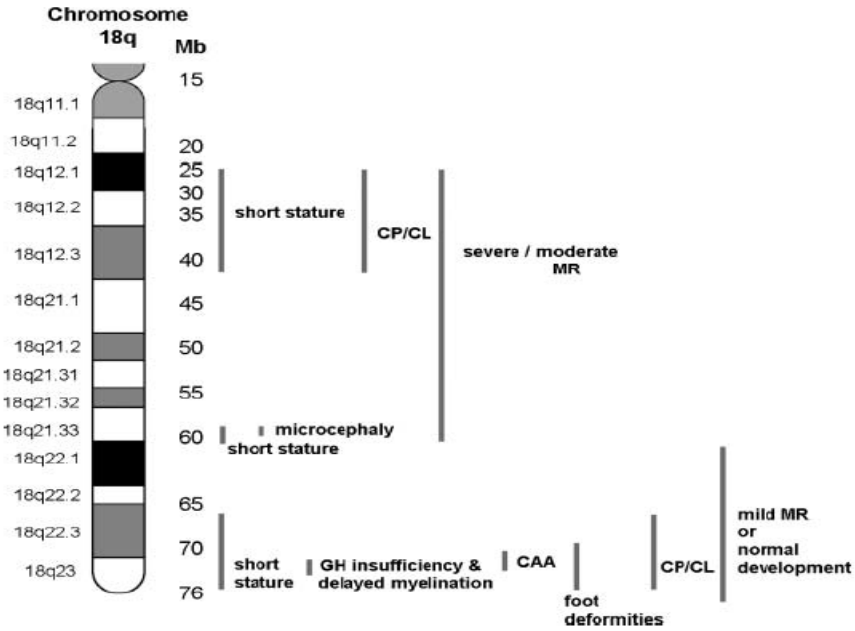

Figure 3. Phenotypic mapping showing critical regions for 18q deletion.

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Reanalysis of whole-exome sequencing data of previously WES-negative children with intellectual disability and/or developmental delay: what are the outcomes of reanalysis in a standard patient care context?

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Background and aim: Although many patients with intellectual disability receive a diagnosis after exome analysis, still many patients remain undiagnosed. This study aimed to inform future reanalysis management by evaluating the yield of WES reanalysis in standard patient care and organization of reanalysis in the Netherlands.

Methods: We collected the data of 159 patients with intellectual disability/developmental delay in which WES analysis and reanalysis were performed in the Leiden University Medical Centre (LUMC) between 1 January 2014 and 31 December 2021. Demographic, phenotypic and genotypic characteristics of patients were gathered and analyzed.

Results: The mean time between the analyses was 3.7 years. A new (likely) pathogenic variant or VUS with a clear link to the phenotype was found in 20 initially exome negative cases, resulting in a diagnostic yield of 12.6%. The majority of newly found variants identified at reanalysis were discovered due to a newly-found gene-disease association. In another three patients, a definite diagnosis was made after reclassification of a variant of uncertain significance found at initial analysis. In patients with dysmorphic features the diagnostic yield was higher compared to patients without these features (yield 27% vs. 6%; p=0.001).

Conclusion: Our results show that reanalysis in patients with ID/DD in standard patient care leads to a substantial increase in genetic diagnoses. Guidelines regarding reanalysis management are necessary and should state the reanalysis indication, frequency and task distribution amongst involved physicians. In addition, the feasibility and appropriateness of systematic reanalysis should be explored.

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MBD6 gene: a promising candidate gene for neurodevelopmental disorders

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Background: The *MBD6* gene encodes the MBD6 protein (methyl-CpG-binding domain protein 6, MIM # 619458). The MBD6 protein is an important regulator of the BAP1 complex. The BAP1 complex is a multiprotein complex that functions as a general transcriptional activator via deubiquitination of epigenetic and transcription factors (Szczepanski, 2021). One of the main constituents of BAP1 complex is BAP1 protein, coded by the *BAP1* gene.

The *BAP1* gene has recently been described as a candidate gene for syndromic neurodevelopmental disorders (Küry, 2022). Depletion of MBD6 protein leads to a global loss of BAP1 occupancy at the chromatin (Tsuboyama, 2022). Thus, we hypothesize that germline variants in *MBD6* gene may lead to a neurodevelopmental phenotype similar to the clinical syndrome caused by germline *BAP1* gene variants.

Methods: We are now collecting clinical data from patients with a neurodevelopmental phenotype and suspected deleterious changes in *MBD6* gene. We are planning to include functional studies in order to determine the molecular effect of the *MBD6* gene variants in our cohort.

Results: So far we have gathered clinical data from eleven patients with potentially deleterious heterozygous, mostly *de novo*, changes in *MBD6* gene and a neurodevelopmental phenotype. Neurological problems occurring repeatedly in this cohort are global developmental delay (6 patients), abnormal behavior including autistic features (6 patients, ASD suspected in 5), epilepsy (3 patients) and dystonia (2 patients). Additionally, dysmorphic features are present in 8/11 patients, with reoccurring reports of prominent forehead (4 patients).

Discussion: Our cohort of patients with suspected deleterious changes in *MBD6* gene has marked similarities with BAP1-related phenotype (global developmental delay, seizures, abnormal behavior; Küry 2022). The data collected so far supports our hypothesizes that *MBD6* gene is a candidate gene for neurodevelopmental disorders.

At this point, we call out to clinicians with patients presenting with neurodevelopmental phenotype and suspicious changes in *MBD6* gene to contact us for collaboration.

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Two affected brothers with Tsukahara Syndrome present with a homozygous deletion in PUS7

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Tsukahara syndrome (MIM 603438) is a very rare disorder characterized by the association of bilateral radio-ulnar synostosis, microcephaly, short stature, scoliosis and mild to severe intellectual disability. Since the initial description by Tsukahara et a.l in 1995, less than 10 families have been reported. Autosomal recessive and X-linked dominant inheritance have been suspected while, so far, no known molecular etiology has been identified in this syndrome. Intellectual developmental disorder with abnormal behavior, microcephaly and short stature (IDDABS) is an autosomal recessive disorder caused by homozygous loss of function variants in PUS7 (MIM 616261). The gene encodes the RNA-independent pseudouridylate synthase 7, an enzyme implicated in post transcriptional modification of RNA and playing an important role in control of gene expression. To date, 8 unrelated families have been described, mostly consanguinous. All patients presented with developmental delay, poor or absent speech, moderate to severe intellectual disability and behavioral abnormalities such as aggressivity, injurious behavior and short temper. Additional features consisted of short stature and poor weight, progressive microcephaly, and variable dysmorphic features including short and smooth philtrum, broad nasal root, full lips with everted lower lip and dental anomalies. We describe a consanguinous family originating from Morocco in which two brothers are suspected of Tsukahara syndrome, a clinical diagnosis we made in 2007 based on typical phenotype associating microcephaly, severe intellectual disability and bilateral radio-ulnar synostosis. Whole exome sequencing was recently performed in both affected boys and their parents. CNV analysis of exome data suggested a deletion of the exon 15 (in a total of 16 exons) of PUS7 in the affected patients. Using droplet digital PCR, we confirmed a homozygous deletion of exon 15 in PUS7 in the boys, present in heterozygous state in their parents, in healthy sister and in healthy brother. This deletion has been previously reported in another Moroccan patient with IDDABS. However, radio-ulnar synostosis was not reported in this patient. In conclusion, this is the first description of a molecular etiology found in two patients with clinical diagnosis of Tsukahara syndrome. We discuss the clinical features of this syndrome and compare it to IDDABS. Finally, we broaden the phenotype related to pathogenic variants in PUS7.

	de Brouwer et al. (2018)			Shaheen et al. (2019)		Darvish et al. (2019)	Naseer et al. (2020)	Han et al. (2022)	Present case	Total cases n=17 (%)
Family	**F1**	**F2**	**F3**	**F4**	**F5**	**F7**	**F6**	**F8**	**F9**	
Ethnicity	Pakistani	Syrian	Moroccan	Saudi Arabia	Egypt	Afghani	Saudi Arabia	North Europe	Moroccan	
Gender	1F/2M	2M	1M	1F	1M/1F	1F/1M	2M	2F	2M	11M/6F
Age at last examination (y)	18/14/7	02-août	3	6	16/14	ND	04-juil	09-juil	22/17	
mRNA variant	c.89_90del	c.1348C>T	exon 15del	c.329_332delCTGA	c.1507G>T	c.382G>A	c.606_607delGA	c.398+1G>T, c.1160C>T	exon 15del	
Protein variant	p.(Thr30Lysfs*20)	p.Arg450*	p.?	p.(Thr110Argfs*4)	p.(Asp503Tyr)	p.(Gly128Arg)	p.(Ser282Cysfs*9)	IVS2+1G>T; p.(Thr387Met)	p.(Trp592*)	
Growth parameters										
Normal birth parametres	+	+	+	+	-	+	+	+	+	15/17 (88%)
Height < - 2 SD	+	+	+	-	+	-	ND	+	+	14/17 (82%)
Weight < -2 SD	+	ND	+	-	+	-	ND	+	+	10/13 (77%)
Progressive microcephaly	+	+	+	+	+	-	+	+	+	15/17 (88%)
Facies										
Smooth philtrum	+	+	+	-	+	ND	ND	+	+	12/13 (92%)
Full lips	+/-	-	+	+	+	ND	ND	+	+	10/13 (77%)
Hypodontia	+/-	-	+	-	-	ND	ND	-	+ microdontia	5/13 (38%)
Neurodevelopmental										
ID (moderate-severe)	+	+	+	+	+	+	+	+	+	17/17 (100%)
Motor delay	-	+	+	-	-	+	+	+	+	11/17 (65%)
Speech delay/Absence speech	+	+	+	+	+	+	+	+/+	+/+	17/17 (100%)
Agressivity	+	+	+	+	+/ND	+	ND	+	+	14/14 (100%)
Brain MRI anomalies	ND	+	-	-	-	ND	+	-	+	6/12 (50%)
Other										
Hearing loss				+	+/-			+	-	
Ataxia								+		
Radio-ulnar Synostosis; Scoliosis									+	

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Triplications of chromosome 1P36.3, including the genes GABRD and SKI, are associated with a developmental disorder and recurrent facial features

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Isolated triplication of chromosomal region 1p36.3 is a rare genomic rearrangement. Here, we describe four patients with variable triplication size (see Figure 1), but with a strong phenotypic overlap, and compare them to previously described patients with an isolated triplication or duplication of this region. The 1p36.3 triplication syndrome is associated with a distinct phenotype, characterized by global developmental delay, moderate intellectual disability, seizures, behavioral problems and specific facial dysmorphic features, including ptosis, hypertelorism and arched eyebrows. The *de novo* occurrence of these triplications demonstrates the reduced reproductive fitness associated with this genotype, in contrast to 1p36.3 duplications which are mostly inherited and which can be associated with similar facial features but with a less severe developmental phenotype. The shared triplicated region encompasses four morbid genes of which *SKI* and *GABRD* are most likely to contribute to the phenotype. De novo heterozygous pathogenic variants in *SKI* are causing Shprintzen-Goldberg syndrome (SGS), which is characterized by mild-to-moderate intellectual disability and hypertelorism as well. Heterozygous gain-of-function missense variants in GABRD were recently associated with neurodevelopmental disorders with behavioral issues, intellectual disability ranging from mild to severe and generalized epilepsy. Further studies are required to explore whether copy number gain of these genes are causing the phenotype in 1p36.3 triplication syndrome.

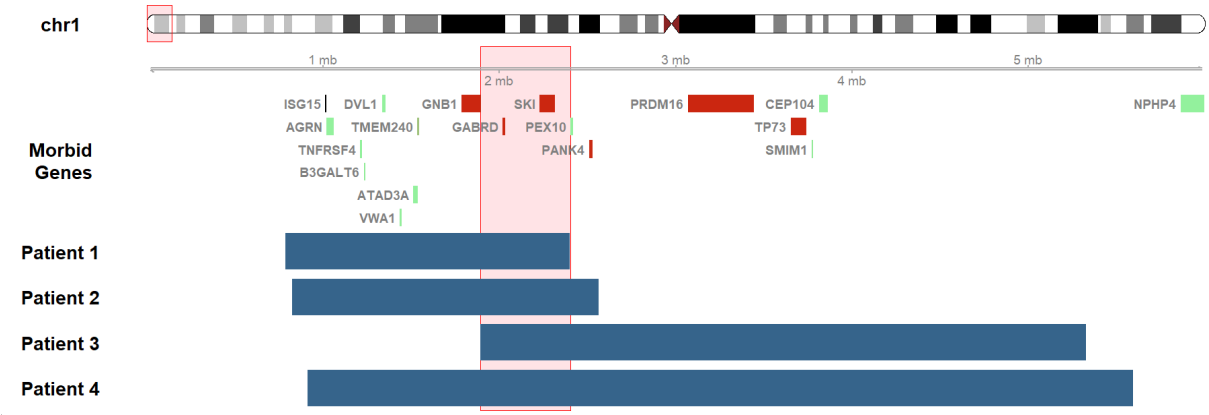

Figure 1 Overview of the triplicated region on 1p36.3 in this study. The colors of the morbid genes correspond to their probability of being loss-of-function intolerant (PLI). PLI scores for genes are coloured on a continuous scale from 0 (green) to 1 (red)

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Two case report of a new recognizable syndrome - DEGCAGS (developmental delay with gastrointestinal, cardiovascular, genitourinary and skeletal abnormalities)

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Introduction: Genomics investigation and applied knowledge is constantly evolving. Every year researchers identify new and promising gene-disease associations. One of the most recent, in 2021, is a novel syndrome – DEGCAGS, caused by biallelic mutations in *ZNF699 (*PMID: 33875846), a gene with scarce previous studies. Only 14 cases have been reported and here, we describe two additional Portuguese cases.

Case report: A two year old boy (Patient 1) was referenced to our genetics unit for investigation of global developmental delay, anaemia, neutropenia, feeding difficulties and retractile testis. He had a coarse facies, sparse hair, synofris, bilateral ptosis and low set posteriorly rotated ears. There was a background of shortened fetal long bones with normal prenatal CGH array. Haematological studies, including bone marrow biopsy, were inconclusive and brain MRI reported leukoencephalopathy, delayed myelination and vermis hypoplasia. At 26 months he was non-verbal and unable to walk.

Whole exome sequencing, plus segregation studies, detected a homozygous variant (c.1327C>T, p.Arg443*) in *ZNF699*. Further evaluation of the literature confirmed the similarities to DEGCAGS patients, including one individual with compound heterozygosity for the same *nonsense* variant (PMID 35205213).

After this diagnosis, our colleagues in haematology recognized a similar phenotype in a seven year old girl (Patient 2), with prior inconclusive NGS multigene panel. She had feeding difficulties, anaemia, dysmorphic facies, small kidneys, hypoplasia of C1 vertebra, congenital deafness and a severe developmental delay (at age 7 she was non-verbal and had ataxic gait, acquired an year earlier). Molecular investigation identified the same homozygous variant, confirming the diagnosis of DEGCAGS.

Discussion: We report two infants with DEGCAGS, homozygous for the same *nonsense ZNF699* variant. The families are unrelated but geographical origin is similar. *ZNF699* variants are presumed as loss-of-function, but no functional studies have been reported.

Few cases have been described and further phenotypic description is needed, including better characterization of the developmental delay, mainly its severity and possible late acquisitions.

This report highlights the constant and swift evolution of genetic knowledge and the importance of revaluating patients with global developmental delay and no diagnosis yet established.

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Homozygous variant c.226C>T p.(Arg76*) in the TRMT10A GENE – a Portuguese case

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Introduction: A new autossomal recessive syndrome characterized by short stature, microcephaly, intellectual disability, epilepsy and early-onset diabetes has been described in association with mutations in the tRNA methyltransferase 10 homologue A *(TRMT10A)* gene that encodes a protein that belongs to the tRNA (Guanine-1)-methyltransferase family.

Case report: We report a Portuguese young patient who presented with short stature, microcephaly with thin *corpus callosum*, *strabismus*, intellectual disability, epilepsy and obesity. The pregnancy was uneventful followed by a full term delivery of a low birth weight infant (1.690 kg, − 2.70 standard deviation score [SDS]). His growth charts demonstrated the head circumference was always under the 5 centile, an abnormal weight gain with obesity and the height became normal in the first years of life, at the present time is under the 5 centile. After birth, we performed an array CGH that was normal and this year the WES identified the homozygous variant c.226C>T p.(Arg76*) in the *TRMT10A* gene. The parents are heterozygous for the same variant.

Comments: *TRMT10A* protein is ubiquitously present but transcription rate is more abundant in human brain and pancreatic islets. This was consistent with the selective involvement of brain (microcephaly and intellectual disability) and pancreatic islets (hyperglycemia and diabetes). Our case presented with prenatal microcephaly and still hasn´t developed diabetes yet. In the literature we could find some cases that the diagnosis was done during the investigation of the early diabetes.

Studies have focused on individual modifications on isolated RNA; RNA modifications exist concurrently in multiple RNA transcripts. Biochemistry and high-throughput sequencing techniques revealed an interaction between a transfer RNA methyltransferase TRMT10A and a messenger RNA demethylase FTO, which influences the methylation levels of a subset of messenger RNAs. However, more studies must be carried on to improve the understanding of these mechanisms.

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Global developmental delay, dysmorphia and severe oropharyngeal dysfunction in a girl with a nonsense mutation in CUX1 gene

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4,5-years old girl was presented at first in the outpatient genetic clinic at the age of 20 months with global developmental delay, hypotonia and dysmorphy. She was born to healthy parents by cesarean section due to impending asphyxia following pregnancy complicated by polyhydramnios, with poor fetal movements. Birth weight 2440g, length 50 cm, Apgar score 4-5-6-7. After birth respiratory insufficiency was diagnosed, requiring mechanical ventilation for 3 days and then CPAP for the next 1.5 months. Since the birth axial hypotonia with limb spasticity, knee and ankle contractures were observed. Dysmorphic features included high forehead with its bitemporal narrowing, micrognathia, low-set ears, constantly open mouth and protruding tongue. A profound oropharyngeal dysfunction has been observed, manifesting as swallowing problems – she is fed exclusively by PEG. In addition she presents with constant drooling, quiet and hoarse voice, and no active articulation, however, she understands all commands and she mastered the basic skills in communication with sign language. It seems that intellectual development appropriate for age. She is able to walk with assistance, her gait is unstable with small steps. Molecular testing included aCGH (normal), MS-MLPA PWS (normal), DM1 (normal); in whole exome sequencing a novel heterozygous molecular variant *de novo* in *CUX1* gene: c.2492G>A, p.Trp831* was found, assessed as pathogenic. Null-allele variants in *CUX1* gene, encoding Cut-homeobox 1 transription factor, which is involved in regulation of dendritogenesis and cortical synapse formation, were reported in patients with global developmental delay (GDD) with possible catch-up development with mild/moderate intellectual disability, but also normal intelligence in some cases [Platzer K et al. Ann Neurol 2018] (ORPHA:178469). The clinical course of the patient presented here is consistent with that described in the literature (GDD with catch-up), but some additional features exist, i.e. severe oropharyngeal dysfunction, which is currently the main health problem, as it influences oral feeding and articulation.

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Interpreting genetic variants in the context of dual diagnosis in a patient with developmental delay

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Introduction: Over the past decade the advances in the molecular-genetic testing technologies has enabled achieving higher rate of accurate diagnosis. At the same time, expanded genetic test methods like large gene panels and whole exome sequencing (WES), enable detection of dual diagnosis, which might be missed during targeted investigations. Correct interpretation of the detected genetic variants is largely driven by careful clinical and biochemical evaluation of the patients.

Case description: We report a four year old male who presented with failure to thrive, left kidney hypoplasia, and feeding difficulties during infancy. The patient has global developmental delay (GDD), impaired speech, excessive drooling, inability to consume solid foods, and difficulty gaining weight. On physical examination, he was observed to have a branchial fistula, periauricular tag, low-set ears, cryptorchidism, thin lips, frontal bossing, and downturned corners of the mouth. The clinical presentation was highly compatible with Branchiootorenal syndrome (BORS), however the facial features were highly suggestive of Coffin-Siris Syndrome. Clinical WES was performed, which revealed following changes: one heterozyous pathogenic deletion of the entire *EYA1* gene, confirming the diagnosis of BORS, and two heterozygous pathogenic variants in *PAH* gene: p.Thr380Met and p.Ala300Ser, associated with phenylketonuria (PKU). Above results raised concerns about the dual diagnosis. Interestingly, the databases of Pediatric Neurotransmitter Disorders (biopku.org) predicted the residual activity of 28% for p.Thr380Met allele and 65% for p.Ala300Ser allele, consistent with total enzymatic activity of approximately 46% - measurement consistent with asymptomic heterozygous state. Subsequent measurement of blood phenylalanine level was within normal range - 17 mg/l (N - 27). Considering total enzymatic activity of the detected *PAH* variants and taking into account absence of the biochemical marker, the diagnosis of PKU was excluded.

Discussion: WES represents the first-line diagnostic test in children with GDD and finding multiple pathogenic variants does not directly confirm the diagnosis, especially for enzymopathies with threshold activity levels, such as hyerphenylalaninemias. It is crucial to interpret genetic test results in the context of the clinical and biochemical findings.The present case underlines importance of the phenotype-to-genotype and genotype-to-phenotype approach (reverse phenotyping) in establishing a precise diagnosis.

Keywords: GDD, BORS, EYA1, PAH, dual diagnoses

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Creatine transporter deficiency: importance of clinical, biochemical and genotype-phenotype correlations

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Introduction: Primary disorders of creatine metabolism (CDDs) are a group of inborn errors of metabolism (IEM), which includes three conditions: guanidinoacetate methyltransferase (GAMT) deficiency, L-arginine:glycine amidinotransferase (AGAT) deficiency and X-linked creatine transporter (CRTR) deficiency. These are clinically heterogeneous disorders characterized by variable degree of global developmental delay (GDD), intellectual disability (ID) as well as with movement disorder, behavior disorder, and seizures. CRTR deficiency is the most common CDD, with around 200 patients reported, accounting for approximately 1-2% of males with X-linked intellectual disabilities. Here, we report two siblings with GDD, ID, speech delay, and ASD with initial positive NBS screening results for acylcarnitines who subsequently were diagnosed with CRTR deficiency on the basis of whole exome sequencing (WES) and biochemical tests. We highlight the importance of clinical, biochemical, and genotype-phenotype correlations in individuals with neurodevelopmental disorders.

Case Presentation: We report 8- and 6-years old brothers with GDD, mild ID, speech delay and ASD. No dysmorphic features or macroorchidism were present. Screening for IEMs showed elevated acylcarnitines for C6, C8 and C10, suggestive of MCAD deficiency. However, there was no clinical correlation. Subsequent whole exome sequencing (WES) revealed maternally inherited hemizygous 2.4 Kb duplication c.(777+1_778-1)_(*1_?)dup in *SLC6A8* gene in both siblings, encompassing exons 5-13. This variant is predicted to result in an in-frame transcript, which preserves the gene's reading frame. Similar-sized duplications have been observed neither in Gcontrol cohorts of enomeAD, nor in the medical literature or disease-related variation databases such as ClinVar, HGMD, or DECIPHER. Additionally, siblings were heterozygous for the paternally inherited *ETFDH* c.740del, p.(Gly247Valfs*6) frameshift variant. In order to determine the pathogenicity of the detected *SLC6A8* variant urinary creatine/creatinine ratio was measured, which was abnormally increased in both siblings. Interestingly, magnetic resonance spectroscopy (MRS) revealed normal levels of creatine peak. Cultured fibroblast analysis for creatine uptake is underway.

Discussion: Presenting case highlights the importance that in children with unexplained GDD / ID, biochemical and genetic studies of primary creatine deficiency disorders should be included. A screening test cannot confirm or rule out a particular condition and further diagnostic tests are needed. In our case patient's positive acylcarnitine profile was explained by heterogenicity for paternally inherited *ETFDH* variant. WES produces a high molecular diagnostic yield, so it should be a first-tier test for children with unexplained GDD. Identification of a hemizygous *SLC6A8* variant of uncertain significance does not confirm or rule out a diagnosis of CRTR. In these individuals, abnormal brain MRS and abnormal urine creatine/creatinine levels in males will be required to support the biochemical diagnosis. Creatine uptake in cultured skin fibroblasts will be needed to confirm the biochemical diagnosis of CRTR deficiency in males. Finally, it's important not to miss a treatable inherited metabolic disorder.

Keywords: WES, developmental delay, NDD, *SLC6A8,* CRTR

Pathogenic variations of gene encoding subunits of the SWI/SNF complex in for 4 patients presenting complex neurodevelopmental disorders without intellectual disability

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Patients with Coffin Siris syndrome (CSS) and Nicolaides-Baraitser syndrome are classically described with intellectual disability (moderate to severe) following developmental delay, organ system anomalies, and dysmorphic feature. It is a heterogeneous group caused by mutation in many genes encoding proteins of the SWI/SNF complex, called BAF complex. ARID1B is the most frequent gene of CSS, and seems associated with more severe developmental delay, where as SMARC related variant, tended to have more severe organ-related complications.

We report 4 patients with pathogenic variants in *ARID1A*, *SMARCC2* (truncating variations) or *SMARCA2* (missense variant), with global developmental delay (walk after 18 months, first words after 3 years) then complex learning disabilities, including attention deficit and language disorder without intellectual disability. All have dysmorphic features, and two of them had minor abnormality of posterior foss on their cerebral RMI, all cardiac evaluation were normal.

Like other genes involving in intellectual disability (ID), CSS is one of the most severe phenotypes for the BAF-related disorder spectrum, and phenotype may be expanded to complex neurodevelopmental disorders without ID, but dysmorphic features.

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Coffin-Lowry Syndrome – A rare disease easier to diagnose

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No presentation at the EuroNDD workshop. Corresponding author: iuliana.coffinlowry@gmail.com

While Coffin-Lowry Syndrome may not be one of the most frequent syndromes it can for sure be, today, one of the most easier to diagnose due to its distinctive phenotype. This is noticeable in early childhood and is modeled through artificial intelligence algorithms. Another important aspect is its mono-genic molecular mechanism.

Through this presentation I want to show you the elements that make this syndrome much easier to diagnose today which eventually leads to improving the lives of so many individuals and their families. These are: the latest progresses made in rare disease knowledge and awareness, the clinical networking, the artificial intelligence, genetic tests availability and affordability and patient advocacy efforts.

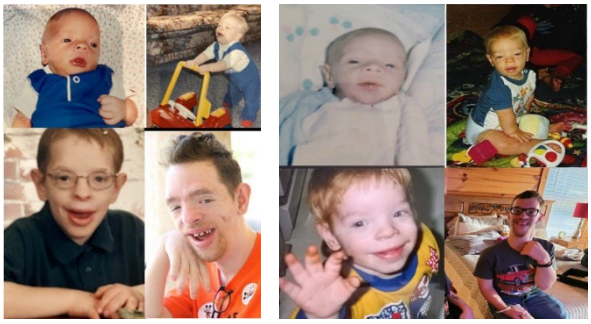
Coffin-Lowry Syndrome is one of the 6000 rare diseases.

It has an incidence of 1: 50 000 cases, which means that we expect more than 300 cases in Romania, 15 000 in Europe and 160 000 worldwide. However only 4 cases are reported to this date in Romania and 500 worldwide are tracked by Coffin Lowry Syndrome Foundation from USA.

All the cases reported in Romania are children below 8 years old and have been diagnosed in the last year. This was possible due to the increased availability and price decreases of molecular tests, as well as to the clinical networking, artificial intelligence and patient advocacy efforts.

The facial gestalt by age makes it possible for clinicians to asses with bare eye, but also use computer-based facial dysmorphology analysis algorithms that are now available in the clinical applications. This can also be crossed checked with the public patient stories that are published by patient advocates – more than 30 stories with pictures.

The presentation focuses on phenotype examples by age: more individuals with the same age, same individual at multiple ages as well as the artificial intelligence models. Below is an example:



Credits for the pictures to: Mary Lindsey Paiter, David Painter, Diana Marie Garvin, Tom O'Brien.

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Recurrence of infant death from severe epileptic encephalopathy without molecular diagnosis

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CASE DESCRIPTION: A healthy non-consanguineous couple had two infant deaths. The first baby boy deceased at 4-month-old with early-onset epileptic encephalopathy with burst-suppression pattern on EEG, resistant to treatment. He also had progressive hypotonia, microcephaly and arthrogryposis. WES revealed a novel heterozygous in *GRIN2B*(NM_000834.3):1852G>A, p.(Val618Ile), of unknown significance, inherited from the mother and grandmother, both healthy. Four years later, a second baby boy was born with the same epilepsy pattern and died at 24 days-old. A second WES in trio did not show any further variants.

DISCUSSION: *GRIN2B* pathogenic variants are known to cause Epileptic Encephalopathy, Early Infantile, 27 (EEEI27; MIM#616139). EEEI27 patients usually present with early-onset encephalopathy irresponsive to treatment. Other findings include microcephaly; dystonic, dyskinetic, or choreiform movement disorder; cortical visual impairment; malformation of cortical development; hypsarrhytmia seen on EEG; and/or malformations of cortical development. Regarding the reported variant, it was not present in gnomAD population database (PM2), nor the literature. It is a missense variant in a gene with low rate of benign missense mutations and for which missense mutation is a common mechanism of a disease (PP2). It is located in a mutational hot spot and critical and well-established functional domain, corresponding to the ion channel-forming reentrant loop implicated in magnesium blockade (PM1). Finally, it locates to the same codon as of known other pathogenic variant with a different amino acid change (PM5). However, this variant was present in the healthy mother. Given the current information and the fact that all reported cases of GRIN2B-encephalopathy were de novo, the variant was classified as of unknown significance.

CONCLUSION: We describe an inherited heterozygous variant in the *GRIN2B* gene in two brothers with early-onset epileptic encephalopathy. To our knowledge, there is no report of incomplete penetrance related to *GRIN2B* gene variants. We need further studies or evidence to solve this family case. A molecular diagnosis would be important for the couple. Without a molecular diagnosis, a precise recurrence risk and reproductive options such as invasive prenatal diagnosis or pre-implantation diagnosis are not possible.

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Syntelencephaly (middle interhemispheric variant): an holoprosencephaly like the others?

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Background: middle interhemispheric variant (MIH) or Syntelencephaly is a subtype of holoprosencephaly (HPE) in which the posterior frontal and parietal areas lack midline separation. While the anatomic and neuroradiologic features of this subtype have been detailed, the clinical and genetic aspects are largely unknown.

Objective: 1) To identify among the 1560 probands of our HPE database (45% live/ 55% fetus), those who presented with MIH; 2) to highlight the differences in imaging, genetics and prognosis between cases with MIH and other forms of HPE.

Methods: Based on review of 39 cases of MIH, including 15 live children and 24 foetuses, neuroimaging/pathological features, clinical data and results of molecular study were collected.

Results: The face was normal in all cases, microcephaly was inconstant, myelination was normal, intellectual disability/ID ranged from absent to severe, spasticity was frequent, as well as hypotonia in the first months and dystonia. No choreoatherosis or endocrine deficits were noted. The *de novo* pathogenic SNVs or CNVs involved mainly the *ZIC2* gene (7 cases), except in one case with a *de novo* class 5 variant in *SHH*. All other variants were class 3, inherited from an asymptomatic parent (*DLL1*, *GLI2*, *LSS*, *SIX3*, *FGF8*). Three patients carried a chromosomal anomaly: trisomy 18, balanced translocation t(7;17)(q36;q23) and a 16p11.2 duplication inherited from the mother along with a *de novo* 16p13.3 deletion in the same patient. Two familial cases were observed. Clinical outcome was more favourable (i.e. without ID) in cases where MIH was isolated, without any microcephaly, and was characterized by Sylvian fissures that did not connect across the midline, with clear separation of both thalami and showing the presence of a residual part of the corpus callosum at the level of its body. ***Conclusion:*** MIH results from a cleavage defect of the telencephalon secondary to dorsal induction defect. If the classical forms of HPE are mainly related to SHH variant, *ZIC2* is the main gene involved in MIH. The prognosis of MIH is better than that of other forms of HPE. However, prospective studies based not only on larger cohorts of patients, but also on precise neuroimaging reports, neuropsychological assessments, as well as WGS analysis and IPS cell models, are required to improve knowledges of this rare brain malformation, especially when prenatal counselling is of concern.

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Could severe microcephaly (< 6 SD) be a good clinical indicator of disease severity and functionality of sequential variants in patients with KIF-11-related congenital microcephaly?

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Introduction: Microcephaly with or without chorioretinopathy, lymphedema, or mental retardation syndrome (MCLMR) (ORPHA:2526) is a rare autosomal dominant neurodevelopmental disorder with variable expressivity. Main sign of disease is a mild-to-severe congenital microcephaly associated with simplified gyral pattern, intellectual disability with a variable degree, ocular defects and lymphedema. Ninety-six patients have been described to carry a point mutation in *KIF11* gene, which encodes a plus-end directed homotetrameric microtubule motor associated with mitosis and translational efficiency.

Methods: We present 2 MCLMR patients with previously unreported variants in *KIF11* gene. We also reviewed the correlation between clinical phenotypes and functional domains of *KIF11* protein according to degree of microcephaly (group 1 – microcephaly < SD 6.0 and group 2 - microcephaly ≥ SD 6.0) in our patients as well as of those described in previously published studies.

Results: In our patients we identified two previously unreported heterozygotic variants *de novo*: P1: *KIF11* c.1294_1296del (p.Glu432del) – VUS in-frame deletion in highly conservated region with prediction to be pathogenic and P2: *KIF11* c.1009dup (p.Ser337PhefsTer8) – likely pathogenic frame-shift duplication in highly conservated region. Our 2 patients with 22 previously published patients with identified *KIF11* variants were classified to the group 1 with the severest degree of microcephaly (24.5% of all analysed patients). Seventy-four previously published *KIF11*-related MCLMR patients were located in the group 2 with milder degree of microcephaly (75.5% of all analysed patients). In the group 1 dominated frame-shift and stop-codon *KIF11* variants (29% and 25% respectively). Only 2 missense *KIF11* variants (8.3%) were identified in this group. Fifty-nine percentage of all variants in the group 1 were located in main functional domain of the KIF11 protein – the kinesin domain. There was a slightly advantage of frame-shift *KIF11* variants in the group 2 with quite equal amount of other types of *KIF11* variants (41% - frame-shift; 21.6% splice/donor site; 20% stop-codon; 16.6% missense). Forty-five percentage of all variants in the group 2 were located in the kinesin domain. There was a higher incidence of coexistence of clinical symptoms triad in patients in the group 1 (group 1: ID 87.5%, retinal changes 79.2%, lymphoedema 58.3% vs. group 2: ID 74.3%, retinal changes 58.1%, lymphoedema 51.3%).

Conclusion: Severe microcephaly (< 6.0 SD) in *KIF11*-related MCLMR patients may be a good clinical marker to predict the location of variants in functional protein domains, as well as to assess the risk of developing intellectual disability and retinal changes in the further clinical course of the disease.

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"TAF2 related to the transcription factor TFIID: a new family and review of the literature"

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Introduction: Initiation of RNA polymerase II-mediated transcription requires the assembly of a preinitiation complex, around the gene promoter region, containing general transcription factors, such as TFIID. *TAF2* encodes for one of the TFIID critical components, the TATA-box binding protein associated factor 2. Causative variants in *TAF2* are associated to Intellectual developmental disorder, autosomal recessive 40 (MIM #615599), phenotypically presenting with severe intellectual disability, pyramidal signs, postnatal microcephaly and thin corpus callosum. To our knowledge, only 11 cases, from 5 families, have been described.

Methodology: Characterization of a new family with 2 affected children, comparison to the previously reported cases and review of the *TAF2* related pathophysiology.

Results: The first child was born from non-consanguineous healthy parents, following an uneventful pregnancy. Birth measurements were in the normal range (weight: -1SD; length: -0,5SD; occipito-frontal circumference: -1SD). For the first three weeks of life, feeding difficulties required nasogastric tube feeding. Initially interpreted as seizures, normal electroencephalogram and brain MRI showed that he had obstructive apneas since birth, due to severe hypotonia and laryngomalacia. At around 3 years old, he maintained hypotonia, along with pyramidal signs, strabismus, microcephaly (-3 SD), hypopigmented macules and severely delayed cognitive and motor development, with no autonomous walking or speech. At 7 years old, he acquired autonomous gait, but with frequent falls. Metabolic studies and CGH array showed no relevant alterations. Exome sequencing performed at 3 years old identified 2 novel variants of uncertain clinical significance in *TAF2*, c.2204T>G p.(Ile735Ser) and c.2933T>G p.(Leu978Arg), in confirmed compound heterozygosity. The parents decided for a new pregnancy and the second boy was born with similar clinical presentation, although with not so severe hypotonia and feeding difficulties. This boy was shown to have the same genotype.

Discussion: Our patients' phenotype, as well as the type of variants identified (missense), seem to match the previous literature reports. The consistent segregation of the variants in the family, with a second affected child, and the deleterious in silico predictions favour the plausible diagnosis related to this gene. We are currently aiming to perform functional studies in order to substantiate this hypothesis. To our knowledge, hypopigmented macules have not been previously described.

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Expending the phenotypic and mutational spectrum of STAG1-related Cohesinpathy

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Cohesinopathies represent rare syndromic form of neurodevelopmental disorders arising from a dysfunction in the cohesin complex, which plays an important role in chromosome segregation, DNA repair, replication and regulates gene expression. Up to date eight cohesin complex genes have been reported in relation to human diseases, with *STAG1* being the most recently discovered one with only 18 patients reported in medical literature so far. Here we describe a 2 years old girl with neurodevelopmental delay, born from non-consaguineous parents. Pregnancy and delivery were uneventful, she was born term with birth weight 3300 gr and birth length 50 cm. She presented with congenital clubfoot and feeding difficulties at birth, which resolved in several weeks. Dismorphic features included micrognathia, open mouth, high palate, low-set ears, anverted nares, wide nasal bridge, thick eyebrows, brachycephaly, high forehead, frontal bossing, strabismus, ptosis, microphtalmia of the left eye with almost complete vision loss. Whole exome sequencing (WES) was performed and a novel c.1183C>T, p.(Arg395*) variant was identified in *STAG1* gene. The variant generates a premature stop codon in *STAG1* exon 12 and is predicted to lead to loss of normal protein function, either through protein truncation or nonsensemediated mRNA decay. To the best of our knowledge, this variant has not been described in the medical literature or reported in disease-related variation databases such as ClinVar or HGMD. In addition, the pLI value of the *STAG1* gene in the gnomAD reference population is 1, indicating that the gene is intolerant to loss-offunction variation. Moreover, parental testing confirmed de novo status of the variant. Our case expands the phenotypic and mutational spectrums of *STAG1* and confirms application of WES as a first-line diagnostic test in individuals with developmental delay and/or multiple congenital anomalies. More studies are needed to define whether genotype-phenotype correlations exist.

Keywords: STAG1, cohesin, WES, developmental delay, NDD

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Generalized lipodystrophy due to diencephalic syndrome as IHPRF1 syndrome's clinical onset in a 10-month-old male: patient report and 14 months of follow-up

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The "NALCN channelosome" is a large ion channel complex consisting of multiple proteins, including NALCN, UNC80, UNC79, and G protein-coupled receptors, which are predominantly expressed in neurons. Several diseases have been associated with the NALCN channelosome: heterozygous *NALCN* variants lead to the congenital contractures of the limbs and face, muscular hypotonia, and global developmental delay syndrome (CLIFAHDD, OMIM 616266), biallelic *NALCN* variants lead to infantile hypotonia, psychomotor delay, and characteristic facies 1 syndrome (IHPRF1, OMIM 615419). Moreover, while failure to thrive (FTT) condition has classically been used to describe children not growing as expected, the diencephalic syndrome is a rare and little-known FTT cause in infants mostly associated with central nervous system tumors without specific laboratory findings. Here we report on a 10-month-old male patient admitted to our Unit for a clinical history of recurrent infections, an almost complete stunting from 6 months of life despite increased caloric intake, and a known finding of supra-sellar/pre-pontine cyst. His clinical picture was mainly characterized by generalized lipodystrophy, dysmorphic features, paroxysmal episodes, predominantly axial generalized hypotonia, periodic breathing and severe psychomotor delay. An extensive multi-specialist diagnostic-differential work-up was performed preliminary to an endoscopic ventricular-cysternostomy. The brain MRI after the surgery documented reduction of the compressive effects on the surrounding encephalic structures and, in particular, on pituitary peduncle and chiasm/optic tracts. After the neurosurgical intervention a progressive increase in growth rate was achieved. Hormonal test showed inadequate cortisol response after ACTH stimulus suggestive for central hypoadrenalism requiring hydrocortisone replacement therapy (10 mg/m2/daily). Interestingly, the metabolic follow-up undertaken showed over the time (pre- and post-surgery) altered urinary oligosaccharides values with increased levels of glucose tetrasaccharide (average 13.7 MoM, RR < 5). A trio clinical exome was performed to further investigate the proband's neurophenotype reveling *NALCN* gene's deleterious variants c.2563C> T (rs376152742) and c.2889 + 2T> A in compound heterozygosity. Studies of children with different FTT causes did not document so far causal relationships between hormonal/cytokine profiles and defined FTT categories. To date urinary glucose tetrasaccharide (Glc4) has been reported as the only available disease burden biomarker for Glycogen storage disease (GSD) type II (acid α-glucosidase deficiency, Pompe disease, PD, OMIM #232300). The degree of its elevation has been also correlated with the severity of the clinical phenotype, age at diagnosis, extent of glycogen accumulation, and to the stage of the disease. Although further studies are needed to understand the correlation between the finding of urinary Glc4 elevation retrieved in our patient and the *NALCN*-related disorders, we propose to extend its screening in this cohort to understand if it could serve as a reliable biomarker also for this condition.

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Meet the 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.

Tjitske Kleefstra is a clinical geneticist dedicated to study underlying mechanisms and clinical consequences of genetic neurodevelopmental disorders. Recently, she is appointed 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 networks.

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.

Dr. Claudine Laurent-Levinson is specialized in physical and rehabilitation medicine and in charge of clinical research for the French Polyhandicap Hospital Federation, Assistance Publique Hôpitaux Paris.

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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.

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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