# Abstract book

## Oral presentations

## EuroNDD 2023

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

*April 20-21, 2023, Amsterdam*

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Dr. Laura De Graaff (NL)
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Prof. Peter Krawitz (DE)

10:15 – 10:45 ***Exchange break with drinks and small snack***

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Chair: Dr. Marie Christine Rousseau (FR) and Dr. Sylvia Huisman (NL)
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Prof. Thierry Billette de Villemeur (FR)

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Dr. Cordula Knopp (DE)

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Chair: Prof. Alain Verloes (FR) and Dr. Sofia Douzgou Houge (NO)
**Invited speakers**
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Dr. Geeske van Woerden (NL)
11:15 – 11:45 **Personalized gene therapy using CRISPR/Cas9 technology**
Prof. Alessandra Renieri (IT)

**Selected abstract**
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Prof. Patrick Edery (FR)

12:00 -12:15 ***Exchange break with drinks and small snack***

12:15 – 13:30 **Parallel session 5 - Ethical, legal and Psycho-social aspects**
Chair: Dr. Claudine Laurent-Levinson (FR) and Dr. Laura de Graaff (NL)
**Invited speakers**
12:15 – 12:45 **Case management for rare diseases and rare disabilities in Europe**
Ms Dorica Dan (RO)
12:45 -13:15 **NDD adults management: Overview in Europe and new challenges**
Dr. Stephanie Miot (FR)



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**Selected abstract**

13:15 – 13:30 **The impact of Sex Chromosome Trisomies (XXX, XXY, XYY) on early social functioning: social attention, affect recognition and Autism Spectrum Disorders symptoms**
Dr. Nienke Bouw (NL)

12:15 – 13:30 **Parallel session 6 - Genes and pathways**
Chair: Prof. Zeynep Tümer (DK)

**Invited speaker**

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Prof. Marco Tartaglia (IT)

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13:00 – 13:15 **LHX2 loss of function causes neurodevelopmental deficits in humans and flies**
Dr. Anne Gregor (CH)

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Prof. Katrin Ounap (EE)

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**Selected abstracts**

14:30 - 14:45 **Update on adults with 22q11.2 deletion syndrome**
Dr. Eric Boot (NL)

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Drs. Jente Verbesselt (BE)

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Dr. Georgia Vasileiou (DE)

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Dr. Anke Van Dijck (BE)

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Drs. Nona Merckx (BE)

15:45 – 16:00 **MED13L knockout in Cerabral organoids leads to a shifted developmental program through abnormal CIS-regulatory element activation**
Dr. Jamal Ghoumid (FR)

16:00 – 16:15 **Menke-Hennekam Syndrome; delineation of domain-specific subtypes with distinct clinical and DNA methylation profiles**
Dr. Leonie Menke (NL)

16:15 – 16:45 **Wrap up with panel of speakers**

16:45 – 17:15 **Final words**
Prof. Tjitske Kleefstra (NL), Prof. Christiane Zweier (CH), Prof. Alain Verloes (FR)



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# Plenary session 1 (Thursday April 20, 13:30 – 15:00)

*- Invited speakers -*

## What can the European Reference Network (ERN) ITHACA do for NDD?

Prof. Alain Verloes, University Hospital Paris, France

**Abstract:** Composed of 71 academic Genetic Centres, ITHACA is the ERN dedicated to rare and complex (neuro)developmental disorders. NDDs are at the heart of ITHACA's action built around several complementary medical, scientific and educational axes, organized around several multidisciplinary WorkGroups. ITHACA has put emphasis on empowerment of patients and families represented by the Patient Advocacy Group that played an overarching role in its co-construction. The Guidelines WG works on Consensus Statements on diseases as Fragile X or Phelan-McDermit syndrome. The NDD WG also develops transversal Guidelines: management of adult ID, care of polyhandicapped persons, challenging psychiatric behaviours... ITHACA supports SysNDD web database and its integration with Orphanet, and contributes to the expansion of ORPHANET encyclopaedia. The T&T WG organizes dedicated webinars and several e-learning tools. By 2023, ITHACA should have its European register (ILIAD) devoted to patients with monogenic NDDs. The research WG publishes calls for collaborative clinical research, and prepares an integrated EU network dedicated to epigenetic abnormalities in development. Born in 2023, EuroNDD, the first EU multidisciplinary Workshop on NDD, should become a recurrent and highly emblematic event summing all ERN activities toward knowledge generation in the care and cure of NDDs.

## Navigating the uncertainties of next-generation sequencing in the genetics clinic

Hilde Van Esch, University Hospitals UZ Leuven, Belgium

**Abstract*:*** Next-generation sequencing (NGS) has significantly increased the chances of finding a genetic diagnosis by enabling a wider and more in-depth look at a patient's genome. Hence, in diagnostic clinical practice, NGS has increased the chances of finding a genetic cause for patients with a wide range of neurodevelopmental disorders to between 40 to 60% when looking at the whole genome. NGS results are, however, often more complex and fluid than those coming from traditional targeted testing, increasing the chances of encountering results with less explanatory power, such as variants of uncertain significance and unsolicited findings. Although no fixed golden standard exist, we will discuss how we can currently deal with variant interpretation and uncertainties.

## Precision diagnostics in NDD - next to next-generation-sequencing

Zeynep Tümer, Copenhagen University Hospital, Denmark

**Abstract:** Precise genetic diagnosis of individuals has been a corner stone of precision medicine enabling new discoveries and approved treatments. However, despite the advances in next generation sequencing based technologies, exome/whole genome sequencing, more than half of the individuals with rare genetic disorders remain undiagnosed. This may be due to e.g. presence of variants outside the coding genome or coding variants difficult to classify, such as variants of unknown significance (VUS). To increase the diagnostic rate several different approaches are being employed, depending on the resources of a given laboratory. In this presentation, some cases and approaches taken will be reviewed.



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# Parallel session 1 – Applied & Emerging Therapies (Thursday April 20, 15:45 – 17:15)

*- Invited speaker -*

**Personal healthcare through braincells on a chip**

Prof. Nael Nadif Kasri, Radboud university medical center, Nijmegen, The Netherlands

**Abstract:** Despite considerable progress in elucidating the genetic architecture of NDDs, a major gap exists between the genetic findings and deciphering the pathophysiology of NDDs. Stem cell technology allow us to generate all cell types present in the brain, in vitro, in a patient-specific manner. However, for most NDDs we currently do not know the exact cellular loci of disease. I will explain our strategy to disentangle the cell type-specific contribution to neuronal network phenotypes in the context of NDDs. We generate composite cultures consisting of well-defined cell types differentiated on micro-electrode arrays (MEA) to probe for neuronal network activity during development. In addition, we combine MEA recordings with transcriptomics within the same experiment (MEA-Seq) to identify molecular pathways that underlie specific neuronal network phenotypes.



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*- Selected abstracts -*

## Making sense of junk: functional enhancers with medical relevance identified by computational analysis and CHIP-STARR-SEQ in neural cell models enable prioritizing non-coding variants from patient whole genome sequencing studies

Ruizhi Deng[1]*, Elena Perenthaler[1]*, Soheil Yousefi[1]*, Anita Nikoncuk[1], Wilfred F.J. van Ijken[3], Eskeatnaf Mulugeta[2] and Tahsin Stefan Barakat[1#]

*Elena Perenthaler, Ruizhi Deng and Soheil Yousefi contributed equally to this work.
[1]Department of Clinical Genetics, Erasmus MC University Medical Center, Rotterdam, The Netherlands
[2]Center for Biomics, Department of Cell Biology & Genetics, Erasmus MC University Medical Center, Rotterdam, The Netherlands
[3]Department of Cell Biology, Erasmus MC University Medical Center, Rotterdam, The Netherlands

Corresponding author: t.barakat@erasmusmc.nl

One of the biggest puzzles in genetics is how to interpret functional relevance of variation in the non-coding genome in the context of Mendelian disease. Transcriptional enhancers are distal non-coding regulatory elements that play crucial roles in the regulation of cell-type specific gene expression, particularly during development and cell differentiation. The massively parallel reporter assay ChIP-STARR-seq enables high-throughput functional annotation of enhancers and quantification of their activity. Tissue-specific screens for enhancer function have the potential to greatly expand our understanding of the role of non-coding sequences in development and disease. To identify enhancers that are likely active during early stages of neural development we generated ChIP-STARR-seq plasmid libraries for various neural cell types using ChIP for H3K27ac, H3K4me1, and selected transcription factors and identified ~15 thousand enhancers showing high activity. These enhancers are linked to genes that are highly expressed during neural development and are susceptible to loss-of-function intolerance. When testing the same neural stem cell (NSC)-derived plasmid libraries in embryonic stem cells (ESCs), we find that enhancers exhibit differential activity in NSCs compared to ESCs. Highly active enhancers specifically in NSCs are linked to genes involved in transcriptional regulation, while ESC-specific highly active enhancers are still linked to genes involved in nervous system development. These enhancers are likely inactive at the endogenous chromatin context as they are not marked by H3K27ac and H3K4me1 in ESCs, but are primed for activity later on during neural development. Together with our previous large scale integrative computational analysis of virtually all available human fetal brain epigenome data and ongoing high-throughput functional validation in zebrafish models, our work expands knowledge on gene regulation during brain development, and identifies non-coding regulatory elements linked to human disease genes, which are primed targets to investigate variants identified by whole genome sequencing to help address missing heritability in neurodevelopmental disorders. We are currently implementing our atlas of regulatory elements for brain development into routine WGS analysis at our center, and would like to discuss possibilities for collaborative efforts within ITHACA and EuroNDD to further advance diagnostics for neurodevelopmental disorders beyond the exome.



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## Antisense oligonucleotide therapies for PLP1-associated hypomyelination of early myelinating structures

Bianca Zardetto[1,2], Marlen Lauffer[1,2], Ronald Buijsen[1], Annemieke Aartsma-Rus[1,2], Willeke van Roon-Mom[1,2]

[1] Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands
[2] Dutch Center for RNA Therapeutics, Leiden University Medical Center, Leiden, The Netherlands

Corresponding author: b.zardetto@lumc.nl

The proteolipid protein 1 (*PLP1*) gene encodes the most abundant protein in the central nervous system (CNS) myelin. The protein plays a role in myelin sheaths maintenance, oligodendrocyte development, and axonal survival. Through a tightly regulated alternative splicing process, it also produces the shorter *DM20* isoform, which only includes exon 3A. Variants in *PLP1* have been associated with disorders of CNS myelin formation that include a spectrum of phenotypes of variable severity. Features of hypomyelination of early myelinating structures (HEMS) have also been described in about 20 patients presenting a relatively mild clinical phenotype. Symptoms include ataxia, progressive spastic paraplegia, and normal to moderately impaired cognition. All cases have been associated with variants found in the *PLP1*-specific exon 3B or splice-altering variants in intron 3. Currently, no disease-modifying treatments are available for these patients, and most therapeutic strategies focus only on managing the clinical manifestations.

Deep intronic, splice-altering variants are ideal candidates for antisense oligonucleotides (ASOs)-based therapies. ASOs are small single-stranded pieces of modified nucleic acids that can bind to target sequences in the pre-mRNA to modulate the splicing process. This strategy offers an opportunity to design a disease-modifying drug that can be customised to the patient's specific variant or to tackle a disease as a whole.

A HEMS patient carrying a deep intronic variant (c.453+159G>A) in intron 3 was identified by our collaborators at the Bambino Gesù Children's Research Hospital in Rome. *In silico* analysis predicted the destabilisation of a double-stranded intronic RNA secondary structure, which was reported previously as having a role in regulating the *PLP1*/*DM20* alternative splicing. Splicing analysis performed in patient-derived fibroblasts confirmed that the presence of the identified variant disrupts the *PLP1* to *DM20* ratio.

For a personalised approach, multiple splice-modulating ASOs were designed to target the deep intronic variant. This proof-of-concept study aims to assess to what extent ASOs can interact with the perturbed secondary structure to restore canonical splicing. Additionally, a different set of ASOs was directed at the internal splice donor site for *DM20* in exon 3 to drive the preferential use of the downstream *PLP1* donor site. This approach would be suitable as a general strategy to target multiple variants hindering the inclusion of the *PLP1*-specific exon. Initial screening was performed in fibroblasts to determine the ability of these ASOs to increase the expression of the *PLP1* transcript. To obtain a more disease-relevant cell type, patient-derived fibroblasts will be converted directly to oligodendrocytes. This model will be used to conduct functional analyses to determine the restoration of protein function after treatment and investigate further the HEMS pathomechanism.

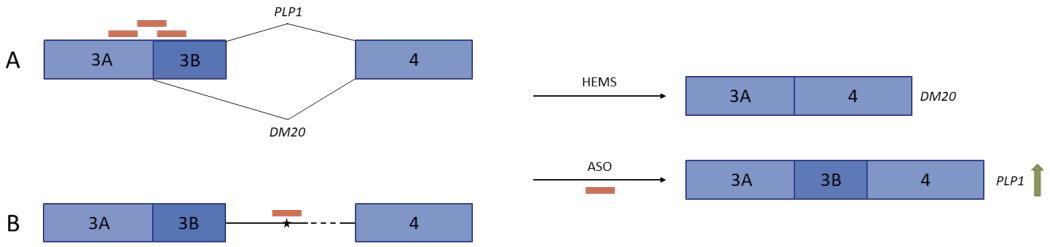


**Figure 1: Schematic representation of the ASO-based strategies** (A) General approach targeting the *DM20* donor site and (B) personalised approach targeting the intronic variant to increase the levels of *PLP1* transcript.



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## Efficacy and tolerance of cannabidiol in the epilepsy treatment in patients with RETT Syndrome: experience in a single center cohort

Béatrice Desnous[1], Thibault Beretti[1], Nathan Muller[1], Nathalie Villeneuve[1], Anne Lépine[1], Robin Cloarec[1], Géraldine Daquin[2], Mathieu Milh[1]

[1] Department of Pediatric Neurology, APHM, Timone Hospital, Marseille, France
[2] Clinical Neurophysiology APHM, Timone Hospital, Marseille, France

Corresponding author: beatrice.desnous@ap-hm.fr

Epilepsy is a major and frequent comorbidity of Rett syndrome, affecting 50 to 90% of patients. Drug resistance in one out of three patients makes treatment challenging and its functional consequences are significant.

We conducted a longitudinal observational study in a monocentric cohort of 46 patients with Rett syndrome and recruited from March 2020 to October 2022 epileptic patients treated with Epidyolex ® (cannabidiol, CBD, 100 mg/ml oral solution) at an initial dose of 5 mg/kg/d with weekly increases up to a maximum dose of 30 mg/kg/d. The phenotype of the patients was characterized by the behavioral scale RSBQ (Rett Syndrome Behaviour Questionnaire ®) and the severity score (Rett Clinical Severity Score ®).

In our cohort, 26 patients had associated epilepsy (26/46 (56%)), and 10/26 (38%) were treated with CBD initiated at a median age of 11 (7-32) years. CBD was associated with a median of 3 antiepileptic drugs (2-4), including clobazam in 50% of cases. The median dose at last follow-up was 15 mg/kg/d. The treatment lasted a median of 13 months (range: 1-32).

CBD reduced the incidence of seizures in 7/10 (70%) of the patients with 1 seizure-free patient, 2 with a reduction of seizures of more than 75%, and 4 with a reduction of more than 50%. No aggravation or adverse effects were observed.

Clinical and RSBQ severity scores were unchanged after CBD. However, half of the patients showed a reduction in their agitation or anxiety attacks. Improvement in spasticity was reported in 4/10 (40%) of patients.

CBD appears to be an interesting therapeutic option in the treatment of drug-resistant epilepsy in Rett syndrome. The tolerance is excellent and the association with Clobazam could be a factor potentiating its effectiveness.



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## Glutamate / GABA modulation as a novel therapeutic target for psychotic and cognitive symptoms in 22Q11 deletion Syndrome

Therese van Amelsvoort[1], Ann Swillen[2], Des Tse[3], Claudia Vingerhoets [1,4]

[1] Department of Psychiatry &Neuropsychology, Maastricht University
[2] Centrum Human Genetics, KULeuven
[3] Department of Cognitive Neuroscience, Maastricht University
[4] sHeerenloo

Corresponding author: t.vanamelsvoort@maastrichtuniversity.nl

22q11.2 deletion syndrome (22q11DS) occurs in 1 in 2000-4000 live births and its phenotype is highly variable including cognitive impairments, and an increased risk for psychosis. Patients with 22q11DS and comorbid psychosis have been found to be less responsive to several dopamine-targeting antipsychotics and more susceptible to their potential adverse effects. Therefore, there is a strong need for novel therapeutics targeting other neurotransmitters to reduce psychotic and cognitive symptoms in these patients. Candidate neurotransmitters are glutamate and γ-aminobutyric acid (GABA). The role of both neurotransmitters in psychosis is increasingly acknowledged and studied. Altered glutamate and GABA transmission in 22q11DS may be caused by reduced proline dehydro-genase (*PRODH*) enzyme activity resulting from haploinsufficiency of the *PRODH* gene. Preclinical studies demonstrated altered glutamate and GABA levels in PRODH knock-out mice. Riluzole, a Food and Drug Administration (FDA)-approved glutamate and GABA-modulating compound, may be a potential candidate drug for treatment of psychosis and associated cognitive decline in 22q11DS.
Therefore we studied in a partially blind, fixed-order cross-over trial the effects of riluzole on psychotic symptoms, cognitive impairments and glutamate/GABA-balance in 22q11.2DS patients.
We hypothesize that:

I) Riluzole improves cognition and alleviates psychotic symptoms.
II) Riluzole will decrease glutamate and increase GABA concentrations in the brain (anterior cingulate cortex (ACC)).

At present 10 subjects aged >16 years with 22q11DS and presenting with psychotic symptoms and/or cognitive impairment have been included. Presence of psychotic and cognitive symptoms have been verified using the Clinical Global Impression-Schizophrenia Scale and the Positive and Negative Syndrome Scale (PANSS). 8-week treatment with placebo is followed by 8-week treatment with riluzole (100 mg. daily). After both intervention periods, participants visited Scannexus, a state-of-the-art 7T-MRI facility, (Maastricht University, https://scannexus.nl/) for measurement of ACC glutamate and GABA levels ($^1$H-MRS) and psychotic and cognitive symptoms. Cognitive functioning has been measured with the Computerized Neurocognitive Battery (CNB) developed by Gur et al. Seven patients currently completed the trial, and two patients have decided to continue riluzole treatment after completion of the study because of the perceived beneficial effects. Detailed, updated clinical and biological results will be presented.



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# Parallel session 2 – Data collection, database, registries, use of AI (Thursday April 20, 15:45 – 17:15)

*- Invited speakers -*

**Phenotypic effects of genetic variants associated with autism beyond diagnosis**

Prof. Thomas Bourgeron, Université de Paris Cité, CNRS, IUF, Institut Pasteur, France

**Abstract**: The heritability of autism is high (>80%), but the genetic architecture is complex made of a combination of common and rare variants. Some conditions such as autism, attention deficit hyperactivity disorders (ADHD), intellectual disability (ID), epilepsy share genetic variants, and the factors contributing to the diversity of the clinical trajectory remain largely unknown. Our previous studies pointed at one biological pathway associated with autism related to synapses. In this presentation, I will discuss our recent results coming from human studies in large populations and genetic isolates as well as mouse studies that shed new light on the inheritance of autism and some of the underlying mechanisms. Finally, I will illustrate how we are currently studying *Resilience* to understand why some carriers of mutations seem to be protected from adverse symptoms while others are severely affected.

**SysNDD and overview on the landscape of NDD**

Dr. Bernt Popp, Berlin Institute of Health at Charité, Germany

**Abstract:** SysNDD is a free website with up-to-date gene-inheritance-disease relationships for neurodevelopmental disorders (NDDs). After browsing tabular data and filtering by phenotypes, gene panels can be downloaded from 1,623 confirmed and 1,256 candidate genes. NDDs can be studied using cross-database comparisons, gene-phenotype correlations, and clustering. Functional and phenotype annotations classify the NDD landscape by inheritance and syndromicity. Recessive inheritance is clinically more heterogeneous and has nearly twice as many entities as dominant inheritance. There is an increase in genes associated with both autosomal inheritance patterns. SysNDD's interoperability will improve diagnostics and care for individuals with rare NDDs.



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*- Selected abstracts -*

## Development of a guideline on the Kleefstra Syndrome within the framework of the European Reference Network ITHACA

Arianne Bouman[1], Carla Sloof[2], Klea Vyshka[3], Tanja Zdolšek Draksler[4], Lara Valerie van Renssen[1], Stacey Bissell[5], Inés Fernández Ulibarri[6], Joyce Geelen[7], Charlotte Gaasterland[8], Tjitske Kleefstra[1]

[1] Radboud university medical center, Donders Center for Medical Neuroscience, Department of Human Genetics, Nijmegen, The Netherlands
[2] ZeldSamen, Dutch patient organization for rare genetic neurodevelopmental disorders, Naarden, The Netherlands
[2] European Reference Network on Rare Congenital Malformations and Rare Intellectual Disability (ERN-ITHACA), Paris, France
[4] Jožef Stefan Institute, Ljubljana, Slovenia/ IDefine USA/ IDefine Europe
[5] School of Psychology, University of Birmingham, Edgbaston, United Kingdom
[6] Asociación Kleefstra España, Madrid, España
[7] Radboud university medical center, Department of pediatrics, Nijmegen, The Netherlands
[8] Emma Children's Hospital, Amsterdam University Medical Centers, Amsterdam, The Netherlands/ Knowledge Institute of the Dutch Federation of Medical Specialists, Utrecht, The Netherlands

Corresponding author: Arianne.Bouman@radboudumc.nl

Kleefstra syndrome (KLFS) is a rare neurodevelopmental disorder (NDD) caused by haploinsufficiency of *EHMT1* (*Euchromatin Histone Methyltransferase 1*) located at chromosome 9q34.3. Key features of KLFS are intellectual disability, developmental delay, psychiatric disorders including autism spectrum disorder, multi-organ involvement and obesity. High heterogeneity is found in both psychiatric and somatic symptoms.

Very few literature studies on KLFS have been published to date (approximately 80, mainly case-reports). However, prevalence has increased due to improved genome wide technologies and currently estimated to be 1:35.000. This widens the KLFS clinical spectrum and the experience by clinical centers worldwide, but due to this global spread, diagnostic approaches and care practices are not properly aligned.

To support clinical decision-making and management, and to provide transparency to patients and caregivers, an evidence-based consensus guideline for KLFS is needed. This fulfills the aim to establish international consensus on molecular investigations, clinical management and surveillance from the prenatal period until adulthood, by merging knowledge and experience.

In many rare NDDs, guidelines are needed, yet rarely developed due to the lack of suitable evidence-based strategies. Within the framework of the European Reference Network for Rare Malformation Syndromes, Intellectual and Other Neurodevelopmental Disorders (ERN-ITHACA) and the KLFS global community lead by IDefine, we therefore designed a new approach for guideline development in rare NDDs. We established an international consortium (total members +- 60 from 17 different countries) comprising professionals and representatives from patient advocacy groups. We based our approach on the prioritization of clinical issues, followed by the prioritization of 12 clinical questions. This prioritization was done using a new developed tool of the Dutch Knowledge institute. Clinical questions were answered with clear recommendations based on literature, grey literature, (clinical and caregiver-reported) registry data, and expert opinion. For most topics, expert opinion was relied on more heavily as little literature was available.

As final product, we aim to present a clinical guideline including a chapter per clinical question, a lay version of the guideline in different languages and a research agenda based on identified knowledge gaps.



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## Real time analysis of patient META_COHORT for neurodevelopmental disorders: an innovative platform proposal

Oliva-Teles NATÁLIA [1,2,3], Jorge PAULA [1,2] , Quintas CÉSAR [4], Huremagic BENJAMIN5, Vandeweyer[6] GEERT, Moreau[7], Yves, Vermeesch[5] Joris R; Harwood ADRIAN J. [8]

[1] Centro de Genética Médica Doutor Jacinto Magalhães, UMIB-Unidade Multidisciplinar de Investigação Biomédica & CBAS-Instituto de
[2] Ciências, Biomédicas Abel Salazar, Centro Hospitalar, Universitário do Porto, Portugal
[3] ITR-Laboratory for Integrative& Translational Research in Population Health, Porto, Portugal
[4] MEDCIDS - Departamento Medicina da Comunidade, Informação e Decisão em Saúde, Faculty of Medicine, University of Porto, Porto, Portugal
[5]Centro Hospitalar Universitário do Porto, 4099-001 Porto, Portugal
[6]Dept of Human Genetics, KU Leuven, Belgium
[7]Dept of Medical Genetics, University of Antwerp, Belgium
[8]ESAT, KU Leuven, Belgium
[9]Neuroscience and Mental Health Innovation Institute (NMHII), Cardiff University, Cardiff UK

Corresponding authors: natalia.teles@chporto.min-saude.pt ; harwoodaj@cf.ac.uk

Copy number variants (CNVs) play an important role in the genetic underpinnings of neuropsychiatric and neurodevelopmental disorders (NDD). However, dealing with different databases, heterogeneity of NDD descriptions and data reporting may be a challenge for scientists, researchers and medical doctors. Following the successful COST ACTION CA16210, "Maximising Impact of research in NeuroDevelopmental DisorderS" (*MINDDS*), which ended in 2022, a COST Innovators Grant, IG16210 was created. This is a pan-European network of scientists, researchers and patient representatives that has been implementing what is designated as *MINDDS-connect*: an innovative data and resource sharing platform for real time analysis of patient meta-cohorts for the NDD and establish mechanisms for data sharing/knowledge exchange.

We aim to identify the needs to create a federated platform, to contribute to the platform´s functionality and utility for federated data analytics across a virtual NDD European metacohort. MINDDS-connect is based on a Widely Integrated NGS Platform (WiNGS) which is a web-based federated data analytics platform aiming to support whole genome analysis of sensitive patient data. It will preserve privacy of sensitive data by storing individual patient data at the local site on secure servers but allows anonymised data analysis across multiple sites by use of data aggregation, the same data-secure blockchain principle that is employed for cryptocurrencies. All IG16210 members will respect FAIR principles and maintain individual privacy and data security. Ultimately, a fully functional multi-user/site, data tool will be developped. We hope that this will become a major analytical tool with which to implement Open Science policy for data sharing in mental health data, facilitating further innovation in clinical knowledge and practise, improved therapeutics and drugs and support development of the Precision Medicine sector.

Acknowledgments: COST Actions: (Maximizing Impact of Research in Neurodevelopmental Disorders) [CA16210, MINDDS]; MINDDS-connect (IG16210) and UMIB, supported by National Funds through the FCT—Fundação para a Ciência e a Tecnologia in the frameworks of the UIDP/00215/2020 and UIDB/00215/2020 projects—Unit for Multidisciplinary Research in Biomedicine—UMIB/ICBAS/UP.

## The genetic landscape of neurodevelopmental disorders in a large cohort of multiplex consanguineous families from Turkey

Esen Gümüslü[1], Evren Gümüs[2], Özlem Öz[3], Melis Özkan[4], Kadri Karaer[5], Arif Ekici[1], Edibe Pembegül Yildiz[4], Nur Aydinli[4], Anita Rauch[6], André Reis[1]

[1] Institute of Human Genetics, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
[2] Sitki Kocman University School of Medicine, Medical Genetics Department, Mugla, Turkey
[3] Harran University School of Medicine, Medical Genetics Department, Sanliurfa, Turkey
[4] Istanbul University School of Medicine, Pediatric Neurology Department, Istanbul, Turkey
[5]Pamukkale University School of Medicine, Medical Genetics Department, Denizli, Turkey
[6] University of Zurich, Inst. of Medical Genetics, Zurich, Switzerland

Corresponding author: andre.reis@uk-erlangen.de

Neurodevelopmental disorders (NDDs) are genetically and phenotypically highly heterogeneous. Autosomal recessive (AR) forms are enriched in families from consanguineous marriages, but these families can present all other forms of inheritance, making a diagnosis challenging. In recent years, diagnostic yield increased from 40% to more than 60% in a recent study, with de novo and X-linked causes in 8-19% of diagnosed cases.

We now investigated a large cohort of consanguineous families with multiple affected individuals with NDDs in order to investigate the genetic landscape focusing on diagnostic consistency within families, which is commonly assumed in such families. We recruited a total of 183 affected individuals from 82 consanguineous families with two or more children with NDDs through clinical genetic and neuropediatric consultations from various academic hospitals in Turkey. Exome sequencing in all affected individuals and their parents allowed identification of pathogenic or likely pathogenic variants for 116 individuals in 85 established or known candidate genes for NDDs. This diagnostic yield of 63% is in line with the most recent report, but was only achieved when also sequencing parents, compared to only 47% when studying affected siblings only. Progress in the field becomes apparent by 8% of diagnoses based on genes published in the last 18 months. In 34 individuals (18.5%) from 23 families, we identified previously described pathogenic variants in 19 genes, indicating a high rate of founder mutations. Similarly to previous studies, we found de novo variants and variants in X-linked genes in 19 cases (10%), and in 54 individuals (29.5%) we found multiple molecular NDD diagnoses. Unexpectedly, only in 14 families (17%) our hypothesis of shared homozygous variants among all affected individuals of that family could be confirmed, as most families presented different molecular diagnoses.

Our study shows that multiplex consanguineous families often represent chance familial aggregation of different genetic disorders and modes of inheritance, requiring individual analysis of each affected child and inclusion of parents in the analysis. Only this way, a diagnostic yield of >60% can be achieved. Founder effects with 19% of cases are relatively frequent, a finding that is only now becoming evident given the growing amount of variant data available. Similarly, progress in gene identification now allows detecting multiple molecular diagnoses, which were seen in 30% of cases, a much higher frequency than in individuals from unrelated parents. Further investigation of novel candidate genes is ongoing and will help further increase the diagnostic yield.



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# Keynote Lecture (Thursday April 20, 18:15 – 19:15)

*- Invited speakers -*

**Why we have the diseases we have**

Han Brunner, Institute of Human Genetics at Nijmegen and Maastricht Medical Centers, The Netherlands

**Abstract**: The landscape of genetic disease is constantly evolving due to the forces of mutation and selection.
This is evident in the case of new dominant mutations that explain the majority severe ID. The fraction attributable to recessive inheritance is <5%, even though up to 20% of individuals in European populations carry an AR ID pathogenic variant. This landscape of many ultrarare ID variants likely reflects the impact of heterozygote expression, and a consequent small reduction in fecundity of heterozygous carriers. Practical consequences are that pathogenic ARID variants are mostly local, and that the impact of consanguinity on ID is particularly strong.



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# Plenary session 2 (Friday April 21, 8:30 – 10:15)

*- Invited speakers -*

**Big Data & Artificial Intelligence**

Wiro Niessen, Dean Faculty of Medical Sciences and Board Member UMC Groningen, The Netherlands

**Abstract:** The combination of big data and artificial intelligence opens up new possibilities for prevention, cure and care, and is likely to change the landscape of our healthcare system. However, the translation from promising research results towards successful and responsible implementation in clinical practice is challenging. In this presentation I will show the opportunities and challenges of big data analytics with AI techniques in health. Applications in the field of improved prognosis in dementia and improved diagnosis and prediction and oncology will be shown. Finally, I will address the challenges of how to successfully integrate these technologies in daily clinical workflow.

**Transition and adult care**

Laura De Graaff, associate professor Internal Medicine for Rare Genetic Syndromes (RGS) and founder of the Erasmus MC Center for adults with RGS in Rotterdam, the Netherlands

**Abstract**: Patients with rare genetic syndromes (RGS), by definition, have combined medical problems affecting multiple organ systems. Due to improved medical care during childhood, more patients now reach adult age. Transition to adult healthcare is often poor and fragmented. Little is known about (management of) medical problems at adult age. Pediatric guidelines contain insufficient data about adults and literature about adults is scarce. This leads to over- and undertreatment and medical complications. At the Erasmus MC Center for adults with RGS, Dr. de Graaff and her team aim to improve quality of healthcare for this complex and vulnerable patient group, combining specialized multidisciplinary care with innovative basic and clinical research. In her talk, Dr. de Graaff will highlight the importance of personalized transition and innovative healthcare for adults with RGS.

**GestaltMatcher, a deep convolutional neural network for the analysis of medical imaging data**

Prof. Peter Krawitz, Head of the Institute for Genomic Statistics and Bioinformatics (W3), University Bonn, Germany.

**Abstract**: GestaltMatcher is a FAIR database for medical imaging data of patients with rare disease that can be used by clinicians as a reference guide and computer scientists to build e.g. AIs for pattern recognition. I will present two recent advances of the GestaltMatcher AI for 1) support in the lumping and splitting problem, and 2) explaining a decision for a certain diagnosis based on the recognized clinical features. Our solution to problem 1) is a cluster analysis in the clinical face phenotype space, and to problem 2) is delineation of HPO terms from the network analyzing the face (Face2HPO).



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# Parallel session 3 – Profound and multiple learning disability

## Friday April 21, 10:45 – 12:00

*- Invited speakers -*

### Communication in Neurodevelopmental Diseases: the importance of developing guidelines

Dr. Gill Townend, University of Huddersfield, United Kingdom

**Abstract**: Communication is fundamental to all we do. For people with complex communication needs, everyone around them must know and understand factors that impact, and strategies, techniques and equipment that facilitate and/or maximise communication potential. All members of the team must have a shared vision and work together to assess communication strengths and needs, determine priorities and goals, and provide appropriate support and intervention. Development of international guidelines helps to ensure minimum levels of knowledge and service provision irrespective of an individual's age or where they live. The Rett Syndrome Communication Guidelines (RSCG) are an example of this. This presentation will provide an overview of the RSCG and how they can act as a model for others.

### Polyhandicap and Neurodevelopmental Diseases

Prof. Thierry Billette de Villemeur, Universités-praticien hospitalier at Sorbonne Université, Hôpital d'enfants Armand Trousseau-La Roche Guyon, Assistance Publique-Hôpitaux de Paris, France.

**Abstract**: What distinguishes polyhandicap among disabilities of children lies in the early coexistence of two mechanisms: multiple and extensive lesions or dysfunctions of the central nervous system and the physiological development and maturation of the brain. Intricate disabilities arise as the brain matures interfering with physiological development leading to evolutionary distortions. The causes are constitutional (genetic, malformative), or acquired early by a clastic or progressive phenomenon (infectious, traumatic, hemorrhagic, anoxo-ischemic, toxic, metabolic...). Thus, polyhandicap includes a deficient or untestable intellect and severe motor disorders resulting in a major loss of autonomy with a dependence for all acts of daily living.



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## Genetic (re-)evaluation to optimize the care of adults with intellectual disability

Cordula KNOPP[1], Robin STEINER[2,3], Eva LAUSBERG[1], Caroline von HOEGEN[2,3], Sabine BUSSE[2] Robert MEYER[1], Katja EGGERMANN[1], Herdit SCHÜLER[1], Matthias BEGEMANN[1], Thomas EGGERMANN[1], Ingo KURTH[1], Jörg B. SCHULZ,[2,3,4], Miriam ELBRACHT[1*], Andrea MAIER[2*]

[1] Institute for Human Genetics and Genomic Medicine, Medical Faculty, RWTH Aachen University, Germany
[2] Medical treatment center for adults with intellectual disabilities and / or severe multiple disabilities, Medical Faculty, RWTH Aachen University, Germany
[3] Department of Neurology, Medical Faculty, RWTH Aachen University, Germany
[4] JARA-Institut Molecular neuroscience and neuroimaging, Forschungszentrum Jülich GmbH and RWTH Aachen, Germany
* these authors contributed equally to this work

Corresponding author: cknopp@ukaachen.de

**Background:** For intellectual disabilities within the context of neurodevelopmental disorders (NDDs) a genetic cause can often be assumed. However, there have only been a few studies that have specifically investigated the detection rates of exome sequencing in adults with neurodevelopmental disorders and in larger exome studies on NDDs adults are often underrepresented. In everyday clinical practice, adult patients with intellectual disability are rarely genetically (re-)evaluated.

In November 2018 the Medical treatment center for adults with intellectual disabilities and / or severe multiple disabilities was founded to offer special care in a multimodal, multiprofessional approach at the RWTH Aachen University Hospital. From the beginning, we have integrated a genetic (re-) evaluation into the assessment and care of these often complex patients in order to find out more about detection rates and the effects of a definite diagnosis on treatment and care.

**Methods:** Between 01.11.2018 and 31.10.2021 60 MZEB patients (age 19-60 years, 26 female, 34 male) with intellectual disability were offered a genetic step-by-step diagnostics (array diagnostics, exome sequencing, in the case of signs of fragile X syndrome also supplemented by a *FMR1* repeat examination). 31 patients (51.7%) had already undergone genetic diagnostics in the past (routine cytogenetic testing (n = 26), array (n = 15), analysis of the *FMR1* gene (n = 12), single gene examinations (n = 10)).

**Results:** In 38 of the 60 (63.3 %) adults, at least one causative genetic alteration was identified. In nine (15 %) patients, a pathogenic copy number (CNV) was already identified in the array diagnostics. In 29 (48.3 %) patients, a pathogenic sequence variant in a known disease-associated gene was identified by exome sequencing. The diagnosis had a direct impact on clinical management in 26 of the 38 diagnosed patients (68.4 %). For example, in nine patients (23.7 %) further investigations under anaesthesia (MRI examination (n = 6), muscle biopsy (n = 2) or lumbar puncture) could be avoided and to five patients (13.2 %) a disease-specific therapy (n = 3, ketogenic diet, galactose-free diet, enzyme replacement therapy) or a drug therapy trial (n = 2, intranasal insulin) could be offered.

**Conclusions:** (Re-)evaluation of genetic diagnosis in adults with NDD that remained etiologically unclear in childhood is highly recommended as this often has an immediate benefit for the patients, facilitates medical care and enables the recording of hitherto long-term courses of rare genetic diseases in adulthood.



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# Parallel session 4 – Mechanisms of diseases, model systems & translational pre-clinical work (Friday April 21, 10:45 – 12:00)

*- Invited speakers -*

**PRISM screen: a tool to screen for functional importance of new genetic variants**

Dr. Geeske van Woerden, Erasmus Medical Center Rotterdam, The Netherlands

**Abstract**: Next generation sequencing is becoming a standard diagnostic method to identify pathogenic genetic mutations in children with an unexplained neurodevelopmental disorder (NDD). A potential pathogenic variant can be identified in the majority of individuals with NDD. However, many of the identified variants are labelled as variants of unknown significance. To establish whether these variants are pathogenic, independent confirmation is needed. The PR*i*SM (Pipeline for Rapid *in silico/in vitro/in vivo* Screening of Mutations) is developed as a functional genomics screen to test the pathogenicity of such variants. During this talk examples of how PR*i*SM has helped identifying novel NDDs will be shown.

**Personalized gene therapy using CRISPR/Cas9 technology**

Prof. Alessandra Renieri, University Hospital in Siena, Itally

**Abstract**: CRISPR/Cas9 system allows targeting and precisely modifying each nucleotide of our DNA, opening new therapeutic windows for genetic disorders. We are this method in monogenic disorders affecting different organs, including brain. To increase targeting to not easily accessible tissues we planned delivery via Adeno-Associated Viral vectors. Tests in iPSC-derived relevant terminal cells demonstrated very good correction, from 20% to more than 80%. In addition to gene/mutation-associated variability, interindividual variability was observed. Specific sequence, chromatin status and TP53 functional polymorphisms are potential contributing factors. The more promising editing's are now transferred to animal model using mice and dogs. Our results stress the relevant potential of the approach for disease treatment.



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*- Selected abstract -*

## DNA Methylation episignature of valproate embryopathy

Seyyedeh Sadegheh Haghshenas[1], Michael Levy[2], Raissa Relator[2], Haley McConkey[2], Jennifer Kerkhof[3], Patrick Edery[4], David Genevieve[5], Audrey Putoux[4], Bekim Sadikovic[2]

[1]Western Univ., London, ON, Canada,
[2]London Hlth.Sci. Ctr., London, ON, Canada,
[3]London Hlth.Sci. Ctr., London, ON, Canada,
[4]Mother and Child Hosp., Lyon, France,
[5]Montpellier University Hospital, Montpellier, France

Corresponding author: patrick.edery@chu-lyon.fr

Valproate is an effective antiepileptic drug and a mood-stabilizer with generally mild side effects. However, it is also recognized as a teratogen, since its consumption during pregnancy has been associated with increased susceptibility of the offspring to congenital anomalies and neurodevelopmental defects, referred to as valproate embryopathy or fetal valproate syndrome (FVS). Diagnosis of FVS can be difficult as there are currently no reliable molecular biomarkers for FVS. Peripheral blood DNA methylation patterns, known as episignatures have been established as stable and accurate diagnostic biomarkers for an increasing number of genetic neurodevelopmental disorders. However, it is currently not known if similar episignatures exist in patients affected by neurodevelopmental disorders that are caused by non-genetic factors, and in particular teratogenic exposures. By assessing a cohort of patients affected by FVS we demonstrate the existence of a highly accurate, sensitive and specific episignature for FVS. We developed a binary classification mode enabling an accurate molecular diagnosis of patients with FVS. We also describe the genome-wide changes in DNA methylation in FVS and compare the changes relative to >120 other genetic neurodevelopmental syndromes with known DNA methylation episignatures. This expands the rapidly growing list of disorders with a known diagnostic episignatures and demonstrates diagnostic utility of EpiSign analysis beyond genetic syndromes.



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# Parallel session 5 – Ethical, legal and Psycho-social aspects

## Friday April 21: 12:15 – 13:30

*- Invited speakers -*

### Case management for rare diseases and rare disabilities in Europe

Ms Dorica Dan, *Romanian National Alliance for Rare Diseases*

**Summary and methodology**: Romanian Prader Willi Association- RPWA, through NoRo center was one of the INNOVCare partners and have developed and tested a holistic care pathway to strengthen the medical, social and educational services in Salaj County, Romania through INNOVCare project. To upscale our experience we have identified that community nurses have the proper background and could support even the most isolated patients living with rare diseases with an adequate training. **Results:**764 community nurses out of 1850 have been trained through ECHO methodology. **Conclusions:** Case management can reduce the waiting time for patients and improve their quality of life.

### NDD adults management: Overview in Europe and new challenges

Dr. Stephanie Miot, University Hospital of Montpellier, France

**Abstract**: Few literature or recommendations are available for NDD adults management. Yet several issues emerge during transitions phases, in particular during aging. After presenting results of a survey about current health care systems for NDD adults in Europe, we will discuss about new challenges with regard to the various geriatric syndromes that NDD adults seem to develop prematurely during their aging.



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## The impact of Sex Chromosome Trisomies (XXX, XXY, XYY) on early social functioning: social attention, affect recognition and Autism Spectrum Disorders symptoms

Nienke Bouw [1,2,3], Hanna Swaab [1,2], Sophie van Rijn [1,2].

[1] Clinical Neurodevelopmental Sciences, Leiden University, Leiden, the Netherlands
[2] Leiden Institute for Brain and Cognition, Leiden, the Netherlands
[3] Department of Child and Adolescent Psychiatry/Psychology, Erasmus MC, Sophia Children's Hospital, Rotterdam, the Netherlands

Corresponding author: j.bouw@erasmusmc.nl

**Background:** Sex Chromosome Trisomies are characterized by an extra X or Y chromosome (XXX, XXY, XYY). Previous research has shown that adults and school aged children with SCT are at increased risk for vulnerabilities in social (cognitive) functioning. As the X and Y chromosomes likely impact brain development from an early age onwards, this study aimed to investigate social attention, affect recognition and Autism Spectrum Disorder (ASD) symptoms in young children with SCT, aged one to seven years old.

**Methods:** A group of 101 children with SCT (aged 1-7 years old; $M_{age}$ = 3.7 years) was included in the study, as well as a sample of 98 control children ($M_{age}$ = 3.7). The SRS-2 was used to study ASD symptoms. Social attention was measured using an eye tracking method that quantifies fixation durations on social information (eyes, faces) in a dynamic paradigm (with two conditions: single faces and multiple faces). Affect recognition was measured using the subtest Affect Recognition of the NEPSY-II neuropsychological test battery. Recruitment and assessment took place in the Netherlands and in the United States.

**Results:** ASD symptoms were increased in children with an extra X or Y chromosome, compared to controls; 27.1% of the SCT group showed ASD symptoms in the clinical range (15.7% in the moderate range, 11.4% in the severe range). Eyetracking results reveal that, on average, children with SCT show less visual attention to social information from the age of three years, compared to children without SCT. Also, impairments in the clinical range for affect recognition were found (32.3% of the SCT group scored in the well below average range); these difficulties were more prominent in older age groups.

**Implications:** Already from a very early age on, SCT may be associated with increased risk for vulnerabilities in social adaptive functioning. These findings suggest that SCT impact the maturation of social information processes already from an early age, and stresses the importance of early monitoring and (preventive) support aiming to promote developmental outcomes of social attention and affect recognition, and related quality of life.



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*- Invited speaker -*

**Novel genetic mechanisms underlying RASopathy spectrum disorders**

Marco Tartaglia, Molecular Genetics and Functional Genomics, Ospedale Pediatrico Bambino Gesù, Rome, Italy

**Abstract**: Signal flow through RAS proteins and the RAF-MEK-ERK (MAPK, hereafter) pathway modulates a wide array of cellular processes in response to external stimuli, and participates in the control of early and late developmental programs. The enhanced activation of this signaling cascade represents a major event in oncogenesis, and underlies a group of clinically related developmental disorders collectively known as “RASopathies”. Based on the relatively high prevalence of some of these disorders, the dysregulation of this signaling pathway represents one of the most common events affecting development.

RASopathies are caused by mutations in genes encoding RAS proteins and functionally related GTPases, regulators of RAS function, modulators of RAS interaction with effectors, or downstream signal transducers of the MAPK backbone. Many of these RASopathy-causing alleles encode proteins with upregulated functional behavior, but with less activating strength compared to those contributing to oncogenesis. In these genes, a largely non-overlapping spectrum of germline and somatic mutations is generally observed. On the other hand, a few of these disorders result from a protein with defective function. In these cases, the implicated proteins negatively control signal flow.

Here is provided an overview on the recently discovered genes implicated in this group of developmental disorders, the underlying molecular mechanisms converging toward the dysregulation of this signaling cascade, and novel emerging clinically relevant genotype-phenotype correlations.

*- Selected abstracts -*

## SEMA6B variants cause intellectual disability and alter dendritic spine density and axon guidance

Amélie CORDOVADO[1], Martina SCHAETTIN[2], Médéric JEANNE[1,3], Veranika PANASENKAVA[1], Anne-Sophie DENOMME-PICHON[4,5], Boris KEREN[6], Cyril MIGNOT[6], Martine DOCO-FENZY[7], Lance RODAN[8,9], Keri RAMSEY[10], Vinodh NARAYANAN[10], Julie R. JONES[11], Eloise J. PRIJOLES[12], Wendy G. MITCHELL[13], Jillian R. OZMORE[14], Kali JULIETTE[15], Erin TORTI[16], Elizabeth A. NORMAND[16], Leslie GRANGER[17], Andrea K. PETERSEN[17], Margaret G. AU[18], Juliann P. MATHENY[18], Chanika PHORNPHUTKUL[19], Mary-Kathryn CHAMBERS[20], Joaquín-Alejandro FERNANDEZ-RAMOS[21], Eduardo LOPEZ-LASO[21], Michael C. KRUER[22,23], Somayeh BAKHTIARI[22,23], Marcella ZOLLINO[24,25], Manuela MORLEO[26,27], Giuseppe MARANGI[24,25], Davide MEI[28], Tiziana PISANO[28], Renzo GUERRINI[28], Raymond J. LOUIE[11], Anna CHILDERS[11], David B. EVERMAN[11], Bertrand ISIDOR[29], Séverine AUDEBERT-BELLANGER[30], Sylvie ODENT[31], Dominique BONNEAU[32], Brigitte GILBERT-DUSSARDIER[33], Richard REDON[34], Stéphane BEZIEAU[34,35], Frédéric LAUMONNIER[1], Esther T. STOECKLI[2], Marie-Laure VUILLAUME[1,3], Annick TOUTAIN[1,3]

[1]UMR 1253, iBrain, University of Tours, Inserm, 37032 Tours, France,
[2]Department of Molecular Life Sciences and Neuroscience Center Zurich, University of Zurich, Zurich 8057, Switzerland,
[3]Genetics Department, University Hospital of Tours, 37044 Tours, France.
Complete list of affiliations available in Cordovado *et al.*, Hum Mol Genet, 2022.

Corresponding author: annick.toutain@univ-tours.fr

In this study, we collected 14 *SEMA6B* heterozygous variants in 16 unrelated patients referred for intellectual disability to different centres. Whereas until now *SEMA6B* variants have mainly been reported in patients with progressive myoclonic epilepsy, our study indicates that the clinical spectrum is wider, and also includes non-syndromic intellectual disability without epilepsy or myoclonus.

To assess the pathogenicity of these variants, we performed in vitro functional studies. Overexpression of some mutated forms of Sema6b in HEK293T cells and in primary neuronal cultures showed a subcellular mislocalisation of SEMA6B protein and a reduced spine density due to loss of mature spines in neuronal cultures. shRNAs targeting Sema6b in neuronal cultures showed that Sema6b knock-down also impairs spine density and spine maturation.

In addition, we conducted in vivo rescue experiments in chicken embryos with the selected mutated forms of Sema6b expressed in commissural neurons after knock-down of endogenous *SEMA6B*. We observed that expression of these variants in commissural neurons fails to rescue the normal axon pathway.

In conclusion, identification of *SEMA6B* variants in patients presenting with an overlapping phenotype with intellectual disability, and functional studies highlight the important role of SEMA6B in neuronal development, notably in spine formation and maturation, and in axon guidance. This study adds *SEMA6B* to the list of intellectual disability-related genes.



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## LHX2 loss of function causes neurodevelopmental deficits in humans and flies

Anne Gregor,[1,2,3,25] Cosima M. Schmid,[1,2,25] Gregory Costain,[4] Chantal F. Morel,[5] Lauren Massingham,[6] Jennifer Schwab,[6] Chloé Quélin,[7] Marie Faoucher,[8,9] Julie Kaplan,[10] Rebecca Procopio,[10] Carol J. Saunders,[11] Ana S.A. Cohen,[11] Gabrielle Lemire,[12,13] Stephanie Sacharow,[13] Anne O'Donnell-Luria,[12,13] Ranit Jaron Segal,[14] Jessica Kianmahd Shamshoni,[15] Daniela Schweitzer,[15] Darius Ebrahimi-Fakhari,[16] Kristin Monaghan,[17] Timothy Blake Palculict,[17] Melanie P. Napier,[17] Alice Tao,[18], Bertrand Isidor,[19] Kamran Moradkhani,[19] André Reis,[20,21] Heinrich Sticht,[22] Care4Rare Canada,[23] Wendy K. Chung,[24,26] Christiane Zweier[1,2,3,26]

[1] Department of Human Genetics, Inselspital Bern, University of Bern, 3010 Bern, Switzerland; [2] Department for Biomedical Research (DBMR), University of Bern, 3010 Bern, Switzerland; [3] Bern Center for Precision Medicine (BCPM), University of Bern, 3010 Bern, Switzerland; [4] Division of Clinical and Metabolic Genetics, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada; Program in Genetics and Genome Biology, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada; Department of Paediatrics, University of Toronto, Toronto, ON M5G 1X8, Canada.
[5] The Fred A. Litwin Family Centre in Genetic Medicine, University Health Network and Mount Sinai Hospital, Toronto, ON, M5T 3L9, Canada; Department of Medicine, University of Toronto, Toronto, ON, M5S 1A8, Canada; [6] Division of Human Genetics, Department of Pediatrics, Warren Alpert Medical School of Brown University, Hasbro Children's Hospital/Rhode Island Hospital, Providence, RI 02905, USA;[7] Clinical Genetics Department, CHU Hôspital Sud, Rennes 35203, France ; [8] Service de Génétique Moléculaire et Génomique, CHU, Rennes 35033, France ; [9] Univ Rennes, CNRS, IGDR, UMR 6290, Rennes 35000, France ; [10] Division of Genetics, Department of Pediatrics, Nemours/Alfred I. DuPont Hospital for Children, Wilmington, DE 19803, USA; [11] Genomic Medicine Center, Department of Pathology and Laboratory Medicine, Children's Mercy Kansas City, Kansas City, MO 64108, USA; University of Missouri-Kansas City School of Medicine, Kansas City, MO 64108, USA; [12] Broad Center for Mendelian Genomics, Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA 02142, USA; [13] Division of Genetics and Genomics, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115, USA; [14] Schneider Children's Medical Center of Israel, Petach Tikvah 49100, Israe; [15] Division of Medical Genetics, Department of Pediatrics, David Geffen School of Medicine, UCLA, Los Angeles, CA 90095, USA; [16] Movement Disorders Program, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115, USA; [17] GeneDx, LLC, Gaithersburg, MD 20877, USA; [18] Columbia University Vagelos College of Physicians and Surgeons, New York, NY 10032, USA; [19] Department of Medical Genetics, CHU Nantes, 44093 Nantes, France; [20] Institute of Human Genetics, Friedrich-Alexander-Universität Erlangen-Nürnberg, 91054 Erlangen, Germany; [21] Centre for Rare Diseases Erlangen (ZSEER), University Hospital Erlangen, Friedrich-Alexander University of Erlangen-Nürnberg (FAU), 91054 Erlangen, Germany; [22] Institut für Biochemie, Friedrich-Alexander-Universität Erlangen-Nürnberg, 91054 Erlangen, Germany; [23] Care4Rare Canada; [24] Departments of Pediatrics and Medicine, Columbia University, New York, NY 10032, USA; [25] These authors contributed equally to this work; [26] These authors contributed equally to this work.

Corresponding author: anne.gregor@dbmr.unibe.ch

*LHX2* encodes the LIM homeobox 2 transcription factor (LHX2), which is highly expressed in brain and well conserved with similar functions across species.
Through international collaboration, we identified 19 individuals from 18 families with variable neurodevelopmental phenotypes, carrying a small chromosomal deletion, likely gene-disrupting or missense variants in *LHX2*. Thirteen variants were shown to be de novo, and one occurred in an affected mother-daughter duo. The affected individuals presented with developmental and/or behavioral abnormalities, autism-spectrum disorder, variable intellectual disability, and microcephaly. A loss-of-function mechanism is likely for the deletion and the ten likely gene-disrupting variants, and we further investigated the functional consequences of six of the seven missense variants by overexpressing mutant *LHX2* in cellular systems. We observed nucleolar accumulation for two variants located within the DNA-binding HOX domain and impaired interaction with co-factor LDB1 for another variant located in the protein-protein interaction mediating LIM domain. Furthermore, we confirmed impaired transcriptional activation by luciferase assay for four tested variants. These results suggest a loss-of-function mechanism also for *LHX2* missense variants. To model the impact of LHX2 loss on neuronal function and behavior, we investigated effects of pan-neuronal knockdown of *LHX2* ortholog *apterous* in *Drosophila melanogaster*. We observed impaired basic locomotor ability as well as reduced daily activity. These observations underscore the importance of apterous in nervous system development and function and thus reinforce a role of human LHX2 in neurodevelopmental disorders.



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## Biallelic KDM8 variants in two sibs with severe failure to thrive, intellectual disability and peculiar facial dysmorphism

Katrin ÕUNAP[1,2], Sally C. FLETCHER[3], Charlotte HALL[3], Tristan J. KENNEDY[3], Sander PAJUSALU[1,2], Monica H. WOJCIK[4], Uncaar BOORA[3], Chan LI[3], Kaisa T. OJA[1,2], Eline HENDRIX[3], Christian A. E. WESTRIP[3], Regina ANDRIJES[3], Sonia K. PIASECKA[3], Mansi SINGH[3], Mohammed E. EL-ASRAG[3, 5], Anetta PTASINSKA[3], Vallo TILLMANN[1,2], Martin R. HIGGS[3], Deanna A. CARERE[6], Andrew D. BEGGS[3], John PAPPAS[7], Rachel RABIN[7], Stephen J. SMERDON[3], Grant S. STEWART[3], Mathew L. COLEMAN[3]

[1] Inst. of Clinical Medicine, University of Tartu, Estonia;
[2] Tartu University Hospital, Estonia;
[3] Institute of Cancer and Genomic Sciences, University of Birmingham, UK;
[4] Broad Institute of MIT and Harvard, Cambridge, MA;
[5] Benha University, Egypt;
[6] GeneDx, Gaithersburg, MD;
[7] NYU Langone Medical Center, New York, NY.

Corresponding author: Katrin.ounap@ut.ee; m.coleman@bham.ac.uk

KDM8 (JMJD5) is a 'JmjC-only' protein hydroxylase that is essential for murine embryonic development and viability. However, no germline variants in JmjC-only hydroxylases, including *JMJD5*, have yet been described that are associated with any human pathology. *KDM8* is a highly conserved gene and is the only member of the JmjC-only hydroxylase family that has been demonstrated to be essential for early mouse embryonic development. Homozygous Kdm8 gene knockout causes severe growth retardation during embryogenesis and lethality during mid-gestation, which has been linked to increased genome instability and activation of the p53/p21 pathway.

We present an Estonian family that experienced two pregnancies associated with intrauterine hypotrophy, oligohydramnion, and growth delay. Post-natal presentation included a severe failure to thrive, relative macrocephaly, facial dysmorphism (a triangular face, high forehead, microretrognathia, a short neck and dysplastic ears), mild brain atrophy, mild to moderate intellectual disability, and muscular hypotonia. Growth hormone replacement therapy had a positive impact on the growth and hypotonia of both affected siblings. The combined clinical symptoms were consistent with a medical classification of syndromic short stature, incl. Silver-Russell, Mabry and Coffin-Siris syndromes. All of them were excluded in routine clinical setting.

To identify genetic etiology of the disease, we performed whole genome sequencing on quadruplicate samples of genomic DNA purified from the two affected siblings and both parents. We discovered biallelic variants in the *KDM8* gene of both affected patients (*c.1086+14_1200_21del* and *c.482G>A*, *p.Cys123Tyr*) that were inherited from the parents and segregated with the disease. The paternally inherited *KDM8* variant is a deletion in intron 7-8 (*c.1086+14_1200_21del*) in close proximity to the boundary with exon 7. This deletion resulting from inappropriate removal of exon 7 deletes amino acids 332 to 362, which reside within a highly conserved and essential section of the JmjC domain that contains a critical catalytic residue (K336) responsible for binding the co-factor 2-oxoglutarate. The maternally inherited *KDM8* variant is a single nucleotide substitution in exon 2 (*c.482G>A*, *p.Cys123Tyr*) that causes the substitution of a highly conserved cysteine residue in the N-terminus of the resulting protein product (CADD=28). Functional analyses demonstrated that biallelic germline *KDM8* pathogenic variants are deleterious to JMJD5 mRNA splicing, protein stability, and hydroxylase activity.

As a summary, we show that the underlying cellular phenotype is associated with increased DNA replication stress and that this is critically dependent on the protein hydroxylase activity of KDM8/JMJD5. This work contributes to our growing understanding of the role and importance of protein hydroxylases in human development and disease.

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# Plenary session 3 – Update on most frequent syndromes & wrap up with panel of speakers (Friday April 21, 14:30 – 16:45)

*- Selected abstracts -*

## Update on adults with 22q11.2 deletion syndrome

Erik Boot [1-3], Claudia Vingerhoets [1,3], Emma von Scheibler [1,3], Ann Swillen [4], Thérèse A.M.J. van Amelsvoort [3]

[1] Advisium, 's Heeren Loo Zorggroep, Amersfoort, The Netherlands
[2] The Dalglish Family 22q Clinic, University Health Network, Toronto, Ontario, Canada
[3] Department of Psychiatry and Neuropsychology, Maastricht University, Maastricht, The Netherlands
[4] Center for Human Genetics, University Hospital UZ Leuven, Belgium, Department of Human Genetics, KU Leuven, Leuven, Belgium

Corresponding author: erik.boot@sheerenloo.nl

**Background:** The 22q11.2 deletion syndrome (22q11.2DS) (OMIM #192430, #188400), the most common human microdeletion syndrome, has an estimated prevalence of 1 in 2000-3000 live births. 22q11.2DS is a multisystem neurodevelopmental disorder associated with variable congenital and later emerging health issues. While historically, most research has focused on children and adolescents, the scientific literature on adults with 22q11.2SDS has been rapidly growing in recent years, and is ample in comparison to most other rare genetic neurodevelopmental disorders. We will highlight recent studies in 22q11.2DS as it pertains to the adult population.

**Results:** An increasing number of psychosocial studies have been conducted in adults with 22q11.DS, reporting on cognitive deficits and poor social judgment and decision-making. Novel research has revealed and/or confirmed associations with endocrinopathies, such as obesity, type 2 diabetes, and hypertriglyceridemia, and neurological disorders, such as parkinsonism (including Parkinson's disease), and other movement disorders. Also, it has now been confirmed that multimorbidity and associated polypharmacy are highly prevalent, present from a relatively young age. Life expectancy is reduced, with mortality most commonly due to cardiovascular causes. Clinical practice recommendations for managing adults with 22q11.2 deletion syndrome have recently been updated.

**Summary:** 22q11.2DS is a complex multifaceted condition, with a growing adult population. Recent findings emphasize the need for coordinated multidisciplinary care involving generalists, medical specialists, 22q11.2 experts and other health care professionals. 22q11.2DS offers a model for precision medicine in rare genetic neurodevelopmental disorders associated with multisystem involvement.



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## Comparison of behavioural and socio-communicative capacities in school-aged children with 16p11.2 deletion and their siblings

Verbesselt J.[1,2], Zink I.[2,3], Breckpot J.[1,4], Swillen A.[1,4]

[1] Department of Human Genetics, Catholic University Leuven, Leuven, Belgium
[2] Department of Neurosciences, Research Group Experimental Oto-Rhino-Laryngology (ExpORL), Catholic University Leuven, Belgium
[3] Department of Oto-Rhino-Laryngology, Head & Neck Surgery, MUCLA, University Hospitals Leuven, Campus Gasthuisberg, Belgium
[4] Centre for Human Genetics, University Hospitals Leuven, Belgium
Corresponding author: jente.verbesselt@kuleuven.be

Background: 16p11.2 deletion syndrome (16p11.2 DS) is a recurrent copy number variant (CNV) that occurs de novo in approximately 70% of cases and confers risk for neurodevelopmental difficulties such as cognitive, behavioural and speech-language problems. The purpose of the current study is to further delineate and compare the behavioural and socio-communicative phenotype of school-aged children with 16p11.2 DS and their non-carrier siblings.
Methods: Behavioural and socio-communicative capacities were assessed by means of three standardized questionnaires completed by parents: Child Behaviour Checklist 6-18 (CBCL), Children's Communication Checklist (CCC-2-NL) and Social Responsiveness Scales (SRS-2-NL). The CBCL evaluates emotional and behavioural problems, whereas the SRS-2 screens deficits in social behaviour associated with autism spectrum disorders (ASD). The CCC-2 assesses everyday communicative situations including speech-language and social abilities. In total, 36 individuals (n=24 with 16p11 DS, n=12 siblings) aged 6-16 years participated. Scores of both groups were compared, as well as to norm group scores.

Results: Compared to the general population, children with 16p11.2 DS show high rates of social responsiveness (83%) and socio-communicative (79%) problems in the mild-moderate to severe range, whereas borderline to clinical behavioural problems are reported in half of the patients. Compared to their non-carrier siblings, children with 16p11.2 DS also score significantly higher on the SRS-2, CCC-2 and the total problem score of CBCL. In children with 16p11.2 DS there is a strong positive correlation between scores on SRS-2, CBCL and CCC-2 (r=0.70).

Conclusion: In this study, school-aged children with 16p11.2 DS show high rates of socio-communicative, social responsiveness and behavioural problems compared to the typical population as well as their non-carrier siblings. These findings point to the high prevalence of autistic traits and diagnoses in this CNV population. Moreover, there is a high comorbidity between socio-communicative and behavioural problems in children with 16p11.2 DS. Patients with difficulties in both domains are vulnerable and need closer clinical follow-up and care.

Key words: 16p11.2 deletion syndrome, copy number variants, deep phenotyping, behavioural phenotype, autistic traits



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## Clinical and molecular spectrum of SMARCC2-associated Coffin-Siris syndrome

Georgia Vasileiou[1], Elisabeth Bosch[1], Bernt Popp[2,3], Esther Güse[1], Cindy Skinner[4], Pleuntje J van der Sluijs[5], Isabelle Maystadt[6] , Annamaria Pinto[7], Alessandra Renieri[7], Lucia Bruno[7], Stefania Granata[7], Carlo Marcelis[8], Ozlem Baysal[8], Dewi Hartwich[9], Laura Holthöfer[9],Bertrand Isidor[10], Benjamin Cogné[10,11], Dagmar Wieczorek[12], Valeria Capra[13], Marcello Scala[14], Rami Abou Jamra[3], Konard Platzer[3], Lauren Carter[15], Outi Kuismin[16], Arie van Haeringen[5], Reza Maroofian[17], Irene Valenzuela[18], Ivon Cuscò[18], Julian Martinez[19], Ahna Neustadt[19], Heather C. Mefford[20], Elaine Pereira[21], Charlotte Close[21], Kwame Anyane-Yeboa[21], Mallory Wagner[22], Mark Hannibal[22], Pia Zacher[23], Isabelle Thiffault[24], Gea Beunders[25], Muhammad Umair[26], Priya T Bhola[27], Erin McGinnis[28], John Millichap[28], Jiddeke van de Kamp[29], Eloise J Prijoles[4], Amy Dobson[4], Amelle Shillington[30], Brett Graham[31], Evan-Jacob Garcia[31], Maureen Kelly Galindo[32], H. Eugene Hoyme[32], Gail Hubbard[33], Catherine Karimov[33], Roger E Stevenson[4], Gijs W E Santen[5], Philippe M Campeau[34], Mariasavina Severino[35], André Reis[1], Andrea Accogli[36]

[1]Institute of Human Genetics, Friedrich-Alexander-Universität Erlangen-Nürnberg, Universitätsklinikum Erlangen, 91054 Erlangen, Germany.
[2]Berlin Institute of Health at Charitè, Universitätsklinikum Berlin, Centre of Functional Genomics, Berlin, Germany; [3]Institute of Human Genetics, UKL University of Leipzig Medical Center, Leipzig, Germany; [4]Greenwood Genetic Center, Greenwood, SC 29646, USA; [5]Department of Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands; [6]Center for Human Genetics, Institute of Pathology and Genetics, Gosselies, Belgium; [7]Genetica Medica, Azienda Ospedaliera Universitaria Senese, Siena, Italy; [8]Department of Human Genetics, Radboud University Medical Center, Nijmegen, The Netherlands; [9]Institute of Human Genetics, University Medical Center of the Johannes Gutenberg University Mainz, Germany; [10]Service de Génétique Médicale, Centre Hospitalier Universitaire de Nantes, Nantes, Pays de la Loire, France
[11]INSERM, CNRS, UNIV Nantes, l'institut du thorax, Nantes, Frances; [12]Institute of Human Genetics, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, 40225 Düsseldorf, Germany; [13]Medical Genetics Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy; [14]Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genoa, Italy; Medical Genetics Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy; [15]Department of Pediatrics, Division of Medical Genetics, Levine Children's Hospital, Atrium Health, Charlotte, North Carolina, USA; [16]PEDEGO Research Unit, Medical Research Center Oulu, and University of Oulu and Department of Clinical Genetics, Oulu University Hospital, Oulu, Finland; [17]Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, University College London, London, United Kingdom; [18]Department of Clinical and Molecular Genetics, University Hospital Vall d'Hebron, Barcelona, Spain; Medicine Genetics Group, Valle Hebron Research Institute, Barcelona, Spain; [19]Division of Genetics, UCLA Institute for Precision Health, Los Angeles, USA; [20]Center for Pediatric Neurological Disease Research, St. Jude Children's Research Hospital, Memphis, TN, USA; [21]Division of Clinical Genetics, Department of Pediatrics, Columbia University Irving Medical Center, New York, USA; [22]Division of Pediatric Genetics, Metabolism and Genomic Medicine, University of Michigan Medical School, Detroit, MI, USA; [23]Epilepsy Center Kleinwachau, Radeberg, Germany; [24]Genomic Medicine Center, Children's Mercy Hospital, Kansas City, Missouri, USA; [25]Department of Genetics, University Medical Center Groningen, Groningen, The Netherlands; [26]Medical Genomics Research Department, King Abdullah International Medical Research Center (KAIMRC), King Saud Bin Abdulaziz University for Health Sciences, King Abdulaziz Medical City, MNGHA, Riyadh, Saudi Arabia; [27]Department of Genetics, Children's Hospital of Eastern Ontario (CHEO), Ottawa, Canada; [28] Division of Neurology, Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL 60611, USA; [29]Department of Clinical Genetics, VU Medical Center, Amsterdam, Netherlands; [30]Department of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
[31]Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN, 46202, USA; [32]Department of Pediatrics, University of Arizona, Tucson, Arizona, USA; [33]Department of Medical Genetics, , Children's Hospital Los Angeles, Keck School of Medicine of University of Southern California, Los Angeles, CA, 90027, USA; [34]Department of Pediatrics, CHU Sainte-Justine and University of Montreal, Montreal, QC, Canada; [35]Neuroradiology Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy; [36]Department of Specialized Medicine, Division of Medical Genetics, McGill University Health Centre, Montreal, QC, Canada; Department of Human Genetics, Faculty of Medicine, McGill University, Montreal, QC, H3A 1B1, Canada. Corresponding author: georgia.vasileiou@uk-erlangen.de

BAFopathies are neurodevelopmental disorders (NDDs) caused by germline variants in BAF complex subunit genes and include Coffin-Siris (CSS) and Nicolaides-Baraitser (NCBRS) syndromes. The discovery of pathogenic variants in another BAF-subunit, SMARCC2, expanded the spectrum of BAF-related NDDs. The *SMARCC2*-associated phenotype is now listed in OMIM as CSS 8. Following the initial characterization of the disorder, only few, scattered reports of *SMARCC2* variants and even fewer clinical descriptions were published. Here we present the largest *SMARCC2* cohort to date, providing a systematic description of clinical and molecular findings from 41 novel cases as well as 24 previously published individuals. The main clinical manifestations include neurodevelopmental delay (85%) with intellectual disability, speech and motor deficits, behavioral disorders (57%), muscular hypotonia (69%), unspecific brain malformations (59%), feeding difficulties (47%) and facial dysmorphic features (45%). Overall, *SMARCC2* cases lack CSS and NCBRS clinical hallmarks, therefore genetic testing is necessary to identify affected individuals.



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We provide compelling evidence that non-truncating and likely gene-disrupting (LGD) variants cause different clinical presentations. Specifically, non-truncating variants are predominantly linked to a severe neurodevelopmental delay syndrome, while LGD variants are primarily encountered in cases with mild/borderline ID or even normal cognitive development (OR: 17.77, 95% CI:4.14-96.03). Our findings indicate that *SMARCC2* missense/in-frame variants cause neurodevelopmental disabilities and neurological defects, while LGD variants are contributory, incompletely penetrant, and may serve as risk factors. Analysis of 45 *SMARCC2* variants, 20 of which are novel, showed that LGD alterations are dispersed across the gene and predominately inherited from phenotypically healthy parents, while non-truncating variants cluster in functional protein domains and mostly occur *de novo*. The two distinct neurodevelopmental manifestations of *SMARCC2*-related disease and the clustering of non-truncating changes suggest that the latter follow a pathomechanism distinct from that of loss-of-function variants, probably with a gain-of-function or dominant-negative effect. Two SMARCC2 functional regions, the SANT and core assembly domain, were discovered to be new mutational hotspots, resulting in reclassification of the herein identified variants as pathogenic. Computational analysis revealed two further gene regions with high constraint and intolerance to amino acid substitutions, thus additional functionally important domains have yet to be defined. Immunofluorescence and quantitative western blot analyses revealed that N-terminal variants show reduced protein expression, similar to the effect of LGD loss-of-function variants. Through 3D structural protein modelling, missense variants in different SMARCC2 functional domains were predicted to change the dynamics of interactions with other BAF subunits, especially with SMARCC1 and SMARCE1. Intriguingly, proximity ligation and co-immunoprecipitation assays did not reveal large-scale impairment of interaction between SMARCC2 mutants and BAF subunits, indicating a more complex underlying molecular pathology. In conclusion, by assembling a large cohort and conducting a systematic review of clinical and molecular data, this study allowed for genotype-phenotype correlations and a better understanding of the *SMARCC2*-associated disorder.



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## Developmental characteristics of children with Helsmoortel-Van der Aa syndrome

Anke VAN DIJCK[1,2], Jessica ROSENBLUM[1], R. Frank KOOY[1]

[1] Department of Medical Genetics, University of Antwerp, Antwerp, Belgium
[2] Department of Primary and Interdisciplinary Care, Disability Studies, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium.

Corresponding author: Anke.vandijck@uantwerpen.be

**Background:** Helsmoortel - Van der Aa syndrome (HVDAS) is caused by de novo mutations in the *ADNP* gene. Patients present with autism spectrum disorder co-morbid with intellectual disability, characteristic facial features and deficits in multiple organ systems. Recently, a large patient cohort of 78 individuals was clinically described. However, a detailed profile of the mental development was lacking. In this study, we aim to describe the cognitive, communicative, motor, social and adaptive development of individuals with HVDAS.

**Methods:** Parents of fifteen Flemish and Dutch subjects agreed to participate in this research project. They filled in the N-CDI and Bayley III standardized questionnaires. The ages of the children ranged from 5 to 15 years. Nine individuals underwent an extensive developmental examination by a specialized team, consisting of a speech therapist, a physiotherapist, and a psychologist in order to obtain a detailed description of the developmental profile of individuals with HVDAS.

**Results:** A significantly lower developmental level was observed in subjects with HVDAS compared to typically developing children. The cognitive, communicative, motor, social-emotional and adaptive developmental levels are affected, with a wide variability.

**Keywords:** *ADNP* gene; Helsmoortel-Van der Aa syndrome; HVDAS



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## Building in vivo human neuronal models for MECP2-related disorders

Nona Laura Lisa Merckx[1,2], Leïla Boubakar[1], Ryohei Iwata[1], Pierre Vanderhaeghen[1], Hilde Van Esch[2].

[1] VIB-KULeuven Center for Brain & Disease Research, Laboratory for Developmental Neurobiology, Leuven, Belgium.
[2] KU Leuven, Human Genetics Department, Laboratory for Genetics of Cognition, Leuven, Belgium.

Corresponding author: nona.merckx@kuleuven.be

Intellectual deficiency and autism spectrum disorders are often caused by mutations in specific genes controlling brain development, but the exact mechanisms linking genetic mutations and deficits are often poorly understood, thereby precluding efficient treatment design. Alterations in the *MECP2* gene are causal in both Rett syndrome (RTT) and *MECP2*-duplication syndrome (MDS), two distinct and noticeably contrasting neurodevelopmental disorders with strongly impaired cognitive function. To date, most of the studies on these diseases have relied on animal models, which has led to substantial progress in the field. However, there are also important evolutionary differences in brain development, between e.g. mouse and human brains, so that the exact impact of mutations in human brain cells remains unknown. This has hampered the translatability of preclinical findings from animal models to humans, in other words, drugs that work in the mouse do not always work in humans.

To overcome this problem, we developed an *in vivo* human neuronal model for RTT and MDS to further decipher the pathophysiological mechanisms. Patient derived induced pluripotent stem cells (iPSCs) are differentiated *in vitro* into cortical neurons and transplanted *in vivo* into the developing mouse brain. In this model the effect of *MECP2* mutations on human neurons can be studied *in vivo* by analyzing neuronal morphology, transcriptomics and epigenomics and testing potential therapies.

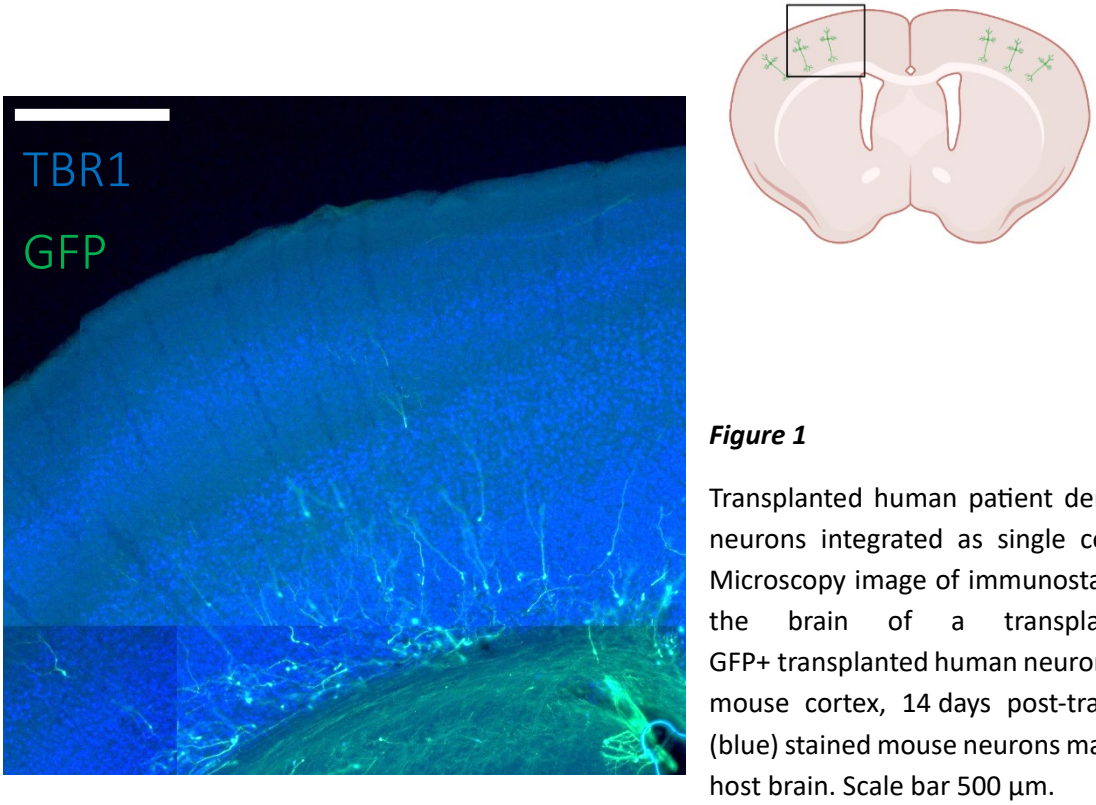




***Figure 1***

Transplanted human patient derived iPSC-derived cortical neurons integrated as single cells in the mouse cortex. Microscopy image of immunostained coronal section from the brain of a transplanted mouse showing GFP+ transplanted human neurons (green) integrated in the mouse cortex, 14 days post-transplantation (DPT). TBR1 (blue) stained mouse neurons mark the cortical layers in the host brain. Scale bar 500 µm.



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## MED13L knockout in Cerabral organoids leads to a shifted developmental program through abnormal CIS-regulatory element activation

Jamal GHOUMID[1], Jerome SIGE[1], Dianne LABOY-CINTRON[2], Ryan Ziffra[2], Nadav AHITUV[2]

[1] Univ. Lille, EA7364 RADEME, CHU de Lille, F-59000 Lille, France
[2] Department of Bioengineering and Therapeutic Sciences, University of California San Francisco, San Francisco, CA, USA

Corresponding author: jamal.ghoumid@chu-lille.fr

The Mediator is a large coregulator complex conserved from yeast to humans. It has emerged as a master coordinator of development and cell lineage determination through interactions with various transcription factors. Pathogenic variants of the gene cause the *MED13L*-syndrome, a neurodevelopmental disorder including intellectual disability. The role of the gene in neurodevelopment is unknown, and the consequences of MED13L variants remain to be deciphered. We developed a MED13L ko cerebral-organoid model from hIPSc and analyzed, at the single-cell level, the transcriptome (sc-RNAseq) and the chromatin accessibility (scATAC-seq). Sc-RNAseq and ScATAC-seq data analysis show that wt organoids produce cortical neurons, and MED13L ko organoids produce only neuroretinal cells. In the MED13L ko model, we observed coordinated activation of O5-O7 and O9 *OTX2* CREs as reported in neuroretinal development, while early specific forebrain *OTX2* CREs, AN1, and AN2, were not activated.
OTX2 is an early markers of both cerebral cortex and neuroretinal development. We suppose that activation of neuroretinal specific CREs driving expression of both latter genes would explain the downstream upregulation of genes involved in neuroretinal differentiation, including CRX, VSX, and USH2A. These results partially explain the shifted developmental program in ko organoids. Based on these data, MED13L is probably critical for proper enhancer activation through neural induction. Neurodevelopmental disorder observed in patients with MED13L pathogenic variant is possibly linked to a global neural gene expression misregulation.



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## Menke-Hennekam Syndrome; delineation of domain-specific subtypes with distinct clinical and DNA methylation profiles

Sadegheh Haghshenas[1]*, Hidde J Bout[2*], Josephine M Schijns[2] , Michael A Levy[1], Jennifer Kerkhof[1], Pratibha Bhai[1], Haley McConkey[1], Zandra A Jenkins[3], Benjamin J Halliday[3], Peter Lauffer[2], Vivian de Waard[4], Laura Witteveen[2], Ella M Williams[3], MKHK Research Consortium, Marielle Alders[5], Raoul C Hennekam[2], Stephen P Robertson[3], Bekim Sadikovic[1,6], Leonie A Menke[2]

[1] Verspeeten Clinical Genome Centre, London Health Sciences Centre, London, ON, Canada
[2] Department of Pediatrics, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands
[3] Department of Women's and Children's Health, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand
[4] Department of Medical Biochemistry, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands
[5] Department of Clinical Genetics, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands
[6] Department of Pathology and Laboratory Medicine, Western University, London, ON, Canada
*These authors contributed equally

Corresponding author: l.a.menke@amsterdamumc.nl

CREB-binding protein (CBP, encoded by *CREBBP*) and its paralog E1A-associated protein p300 (*EP300*) are involved in histone acetylation and transcriptional regulation. Variants that produce a null allele or disrupt the protein's catalytic domain cause Rubinstein-Taybi syndrome, while in-frame pathogenic variants in parts of exons 30 and 31 cause phenotypes recently described as Menke-Hennekam syndrome (MKHK). To distinguish MKHK subtypes and define their characteristics, molecular and extended clinical data on 82 individuals (54 unpublished) with variants in CBP (n=71) or p300 (n=11) (NP_004371.2 residues 1705-1875 and NP_001420.2 1668-1833, respectively) were summarized. Additionally, genome-wide DNA methylation profiles (episignatures) were assessed in DNA extracted from whole peripheral blood from 53 individuals. Most variants clustered closely around the Zinc binding residues of two Zinc finger domains (ZZ and TAZ2) and within the first $\alpha$-helix of the fourth intrinsically disordered linker (ID4) of CBP/p300. A domain-specific episignature was discerned for the ZZ domain in CBP/p300 (found in 9/10 tested individuals) and TAZ2 domain in CBP (in 16/20) and was further refined for ID4 in CBP/p300 (in 21/21). Phenotypes included intellectual disability of varying degree and distinct physical features for each of the regions. We conclude that MKHK consists of at least three domain-specific (MKHK-ZZ, MKHK-TAZ2, and MKHK-ID4) rather than *CREBBP/EP300* gene-specific subtypes, based on distinct phenotypes and domain-specific episignatures. Our data furthermore show that episignatures provide a powerful tool to discern the existence of different entities within a gene or across a family of paralogous genes.



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# Meet our speakers

**Therese van Amelsvoort** is an academic psychiatrist who have obtained funding for, and supervised over 25 PhD projects. She is professor in transitional psychiatry. She has been running the National Adult 22q11DS clinic for 20 years and is member of the COST network MINDDS on neurodevelopmental disorders. She is the initiator of @ease, the Dutch version of the successful Australian Headspace initiative, easy access youth mental health centers serving prevention and early detection. She is leading the Mental Health academic research group of Maastricht University. She runs (and initiated) a youth mental health clinic bridging the gap between child & adolescence and adult services. She has more than 20 years clinical and academic experience in the field of 22q11DS, and more recently including 22q11Dup. She is part of several collaborative research networks including IBBC, ENIGMA, GROUP, PSYSCAN, MINDDS.

**Stefan Barakat** is a clinical geneticist, and trained experimental biologist that is heading since 2017 a research team at the Clinical Genetics department of the Erasmus MC University Medical Center. His team focusses on deciphering novel causes of neurodevelopmental disorders, focussing on the role of the non-coding genome and new disease genes. Using functional genomics and other approaches they are studying the gene regulatory landscape in cells representing neurodevelopment. The long-term goal is to translate their research findings to the clinic, where we aim to develop novel diagnostic and therapeutic approaches for patients focusing on the so far, so often, neglected non-coding regions of the human genome. With his dual position, of both being a scientist and a practicing clinician, he is in a unique position as an important bridge between research and clinic, ultimately leading to advancements for patients. Next to his interest in gene regulation, the group applies disease modelling for neurodevelopmental disorders using genome engineering, induced pluripotent stem cells, cerebral organoids, and zebrafish.

**Thierry Billette de Villemeur** is pediatrician, professeur des universités-praticien hospitalier at Sorbonne Université, Hôpital d'enfants Armand Trousseau-La Roche Guyon, Assistance Publique-Hôpitaux de Paris. Specialized in neuropediatrics, his clinical and ethical practice and research focus on the neurological and intellectual development of children, neurodegenerative diseases, antenatal diagnosis of fetal brain abnormalities, polyhandicap/PIMD, and palliative support and end of life support of these children when they are concerned.

**Erik Boot** is a physician specialized in intellectual disability medicine and works at the multidisciplinary 22q11.2 clinics for adults at 's Heeren Loo and Maastricht, in the Netherlands. His clinical and research interests include genetic neurodevelopmental disorders, in particular 22q11.2 deletion syndrome and Smith-Magenis syndrome. He is an advisor for the Dutch 22q11.2 family network and 22q11.2 Society. He has authored and co-authored several peer-reviewed journal articles and book chapters, including the recently updated clinical practice recommendations for managing adults with 22q11.2 deletion syndrome.

**Arianne Bouman**, MD, is PhD student at the department of Human Genetics, Radboudumc Nijmegen, under the supervision of Prof. Dr. Tjitske Kleefstra, Dr. Joyce Geelen and Prof. Dr. Hilgo Bruining (Amsterdam UMC). Her main focus in this PhD trajectory is the BRAINmodel project, a Dutch multicenter study focused on treatment development in several monogenetic neurodevelopmental disorders, including Kleefstra syndrome. As a side project, she is involved in the development of the first international ERN guideline on Kleefstra syndrome.

**Thomas Bourgeron** is Head of Unit Human Genetics and Cognitive Functions, Université de Paris Cité, CNRS, IUF, Institut Pasteur. His laboratory gathers psychiatrists, neuroscientists, and geneticists to better understand autism. His lab discovered mutations in genes highlighting the key role of the synapse in autism. His group gathers the genetic and database work packages for the European projects (AIMS2-Trials, CANDY, R2D2-MH). They develop methods for analysing large dataset as well as new paradigms for characterizing mouse social and vocal behaviours. He is a member of EMBO, the French Academy of Sciences, the Academia Europaea and the National Ethical Committee from France.



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**Nienke Bouw** studied 'Developmental Psychopathology in Education and Child Studies' at Leiden University. After graduating with honors, Nienke started her PhD research in 2017. The central goal of her project was to study the impact of Sex Chromosome Trisomies on early social (cognitive) development, aimed to identify early markers of developmental risks, leading to social vulnerabilities and associated psychopathology. Since obtaining her PhD, Nienke has been working as child psychologist at the outpatient clinic for Child and Adolescent Psychiatry at the Erasmus MC/Sophia Children's Hospital in Rotterdam.

**Han Brunner** is Head of the Institute of Human Genetics at Nijmegen and Maastricht Medical Centers, where he pioneers genomic technologies in medical genetics. His group identified genes for CHARGE, EEC, and Robinow syndrome. He also identified a human behavioural gene. Work showing that new mutations are the main cause of intellectual disability, led to the acceptance of exome sequencing as a first-tier test in neurodevelopmental disorders Recently, his group established the landscape of autosomal recessive diseases in European populations.

**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.

**Beatrice Desnous** is a child neurologist at the University Hospital for children of La Timone in Marseille, France. Her research deals with pathophysiology of neurodevelopmental disorders, early detection of neurodevelopmental disabilities and early intervention

**Anke van Dijck** graduated as an adult neurologist in 2019. She did a PhD about therapeutic strategies for neurodevelopmental disorders, at the Cognitive Genetics Group in the Center of Medical Genetics, Antwerp. The focus of her research was the treatment of the fragile X syndrome and the clinical characterisation of the Helsmoortel - Van der Aa syndrome. Currently, she is the coordinator of the Disability Studies research group at the University of Antwerp. She also works in a rehabilitation hospital.

**Patrick Edery** is a professor of paediatrics and genetics. He trained in the genetics team at the Necker-Enfants Malades Hospital in Paris, France. His research contributed to the identification of several genes responsible for developmental abnormalities, including the gene responsible for a congenital defect of the terminal intestine, Hirschsprung's disease (Edery P et al, Nature 1994) and the gene responsible for microcephalic dwarfism type 1 (MOPD1), a small non-coding gene involved in the splicing of a subset of introns in the genome (Edery P et al, Science 2011). Since then, his work has focused on understanding the pathophysiology of this severe microcephalic dwarfism, with the recent description of ciliary defects associated with this developmental disorder (Khatri et al, PNAS 2023). Patrick Edery created and directed the genetics department of the University Hospital of Lyon, France since 2005, which he currently co-heads, and he created and heads the research team in neurodevelopmental genetics (GENDEV) of the Lyon Neuroscience Research Centre (CRNL), France. In 2007, during the first national plan for rare diseases, he also obtained the labeling of the rare disease reference centre (CRMR) for developmental anomalies (CLAD Sud-Est), which he still coordinates. The CLAD Sud-Est is attached to the AnDDI-Rares network and the ERN ITHACA.

**Hilde van Esch** is a paediatrician and clinical geneticist from training and staff member at the Centre for Human Genetics at the University Hospitals UZ Leuven, where she covers a broad field of medical genetics, with specific interest in intellectual disability, neurology and syndromology  As assistant Professor at KU Leuven, she heads the Laboratory for the Genetics of Cognition. Her research is focused on neurodevelopmental disorders and congenital brain malformations.



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**Jamal Ghoumid** is Professor for clinical genetics at the University of Lille, France. He is the head of the research team RADEME. Jamal is an expert of the genetic of the intellectual disabilities. His research topics are the anomalies of the genic regulation underlying genetic diseases, with a special focus on MED13L. Along with his team and collaborators, Jamal take advantage of the cerebral organoid model to decipher the role of this gene in the brain development.

**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.

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

**Adrian J Harwood** is Co-Director of Cardiff University's Neuroscience and Mental Health Innovation Institute (NMHII), a multidisciplinary research centre of neuroscientists, psychologists, human geneticists, and clinicians. His research studies patient derived and CRISPR-engineered induced pluripotent stem cells (iPSCs) to study psychiatric disorders, including those associated with Rare Genetic Syndromes. These activities include projects with the pharmaceutical industry and the founding of MeOmics, a university spinout company based on large-scale patient iPSC-based neuronal assays. He chairs MINDDS, research consortium MINDDS to establish patient meta-cohorts of CNV carriers with an associated NDD.

**Cordula Knopp** is a clinical geneticist and works as a consultant at the Institute for Human Genetics and Genomic Medicine at the RWTH Aachen University hospital. She has studied medicine in Lübeck, Rostock, Bergen (NO) and Bristol (GB) and completed her specialized training at the RWTH Aachen University hospital. One of her research interests is the course of rare genetic syndromes in adulthood.

**Peter Krawitz** is Head of the Institute for Genomic Statistics and Bioinformatics (W3), University Bonn, Germany. Peter was trained as a physicist and physician in Munich and continued with a residency in Medical Genetics Berlin. As a clinician scientist, he identified the disease-causing gene for Hyperphosphatasia with Mental Retardation and is since then interested in of glycosylphosphatidylinositol biosynthesis defects. After establishing analysis platforms for genome data he realized these tests will also require better and faster phenotyping. He therefore focused his research on deep learning methods to analyze medical imaging data.

**Leonie Menke** is a Developmental and Genetic Pediatrician at Emma Children's Hospital and the current President of the national board of the Developmental and Genetic Pediatricians. She leads the Amsterdam UMC Expert Centre for Developmental disorders (AECO) and is head of the Expert Centre for children with Marfan syndrome and related disorders. Her research focusses on care for rare genetic intellectual disability, also for those children in whom no genetic cause has been found.

**Nona Merckx** is doing her PhD at KU Leuven and the Center for Brain and Disease Research (VIB) in Belgium in the laboratory of Hilde Van Esch and Pierre Vanderhaeghen. Her research focuses on developing in vivo human neuronal models using xenotransplantation to study MECP2 related neurodevelopmental syndromes. She studied Biomedical Sciences at Maastricht University, Advanced Genetics at the Autonomous University of Barcelona (UAB) and studied the function of the gene NCOA7 in Autism Spectrum Disorder (ASD) during her thesis at Boston Children's Hospital.



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**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.

**Nael Nadif Kasri**, PhD., studied biochemistry followed by a PhD (2004) at the KU Leuven. After his PhD he worked as a postdoctoral researcher (2010) at Cold Spring Harbor Laboratory, where he studied the role of disease genes in excitatory synapses. In 2011 he received the Hypatia Fellowship from the Radboud Medical Centre and started his independent research group. He currently is professor of Medical Neuroscience for Neurodevelopmental Disorders at the Department of Human Genetics. The focus of his current research is to understand the synaptic basis of neurodevelopmental disorders using in vitro human stem cell-based models.

**Wiro Niessen** is Dean of the Faculty of Medical Sciences, University Groningen and Board Member of the UMCG. He is professor of AI in Medical Imaging and Health and has expertise in the development and implementation of AI in healthcare. He is fellow and was president of the MICCAI Society. In 2015 he received the Simon Stevin award, the largest prize in the Netherlands in Applied Sciences. In 2017 he was elected to the Royal Netherlands Academy of Arts and Sciences.

**Katrin Ounap** is since 01.09.2010 professor in Clinical Genetics at Institute of Clinical Medicine, Faculty of Medicine, University of Tartu, Tartu, Estonia. Since 01.03.2022 Senior Medical Doctor in Medical Genetics at Genetic and Personalized Medicine Clinic, Tartu University Hospital. Holds licence in paediatric and medical genetics. Defended PhD degree in 1999 at the University of Tartu on Phenylketonuria in Estonia. She has supervised 17 and supervising seven PhD students. Published over 160 publications.

**Bernt Popp** is currently a senior physician and researcher at Berlin Institute of Health at Charité (BIH.Prior to relocating to Berlin, he worked as a human geneticist in Dresden, where he headed the outpatient genetics clinic, Leipzig, and Erlangen, where he completed his residency. Rare diseases of neuronal development, rare tumors, and the kidney are his areas of scientific interest within the field of human genetics. He particularly enjoys bioinformatics work involving high-throughput sequencing data analysis and the curation of genetic diseases, variants, and genes.

**André Reis** is a physician by training and the director of the Institute of Human Genetics at the University Hospital Erlangen in Bavaria, Germany, where he coordinates the local ITHACA activities. His research interest is in gene identification and pathophysiology of inherited disease along with correlation of genotype and phenotype with a major focus on neurodevelopmental disorders. His research group identified the genetic basis and contributed to the clinical delineation of numerous syndromes and disorders.

**Alessandra Renieri** is full Professor of Medical Genetics at the University of Siena and Director of Medical Genetics at Azienda Ospedaliero-Universitaria Senese. Her main research interest is the study of the genetic basis of rare diseases, especially Rett syndrome and other conditions with intellectual disability, Alport syndrome and rare cancers. Since 2017 she focused on the translation of gene editing using CRISPR/Cas9 to clinical practice. She is running different gene editing projects related to Rett syndrome, Parkinson and Alport syndrome. Since 2019 she is Member of The EMA Committee for Advanced Therapies (CAT).

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

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

**Natália Oliva Teles** is a Doctor in Bioethics, a Master in Bioethics and Medical Ethics and has a Honours Degree in Biology. She is a Clinical Laboratory Geneticist and Head of Cytogenetics in a large University Hospital in Porto, Hospital de Santo Antonio, and an Auxiliary Prof. in Bioethics, Faculty of Medicine/University of Porto. She is a member of an International Network Chair in Bioethics, belongs to two COST Actions and is a Member of two Ethics Committees. She was Treasurer of EBMG/ESHG (2019-2022).

**Annick Toutain** is clinical geneticist at the university hospital and professor of medical genetics at the faculty of medicine of Tours. He was the head of the Genetics Department and still coordinates three centers for rare diseases, concerning malformations, intellectual disability and genetic deafness. He is member of a research unit 'iBrain', in the team working on neurogenomics and neuronal pathophysiology. He is particularly interested in neurodevelopmental disorders, both from a clinical point of view and from a scientific point of view.

**Gillian Townend,** PhD, MPhil, BMedSci (Speech), is a Senior Lecturer (Speech and Language Therapy) at the University of Huddersfield, Project Lead for Rett UK's Communication and Education Team, and a freelance researcher at the Rett Expertise Centre Netherlands. Dr Townend led the project team behind the development of the international *Rett Syndrome Communication Guidelines* which were published in 2020. Her other research interests include development of alternative methodologies for assessing language and cognition, eye tracking and the functional use of eye gaze for communication, and language processing in Rett syndrome.

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



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**Georgia Vasileiou** obtained her undergraduate degrees in Biology and Medicine, followed by PhD in the Department of Biochemistry in the University of Thessaloniki, Greece. She served as resident in the Institute of Human Genetics, and for one year in the Neuropediatric Department at University Hospital Erlangen, Germany. Currently, she is senior clinician and group leader in Human Genetics in Erlangen. Her research focuses on delineation of clinical and molecular spectrum of neurodevelopmental disorders, particularly the BAFopathy Coffin-Siris syndrome.

**Jente Verbesselt** is a speech-language pathologist and audiologist and obtained both master's degrees at the University of Leuven. She is currently working as a PhD researcher in the laboratory for Behaviour and Neurodevelopent at the Department of Human Genetics of KU Leuven under the supervision of Prof. Dr. Ann Swillen, Prof. Dr. Inge Zink and Prof. Dr. Jeroen Breckpot. Her PhD project focuses on deep phenotyping of speech, language, cognition, and behaviour in patients with recurrent copy number variants.

**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.

**Geeske van Woerden** completed her PhD at the Dept of Neuroscience, Erasmus MC, in the lab of Prof. Elgersma, studying the role of CAMK2 in the brain. After a 2-years postdoc period, she returned to the Erasmus MC starting her own research group focusing on the role of CAMK2 in normal brain function and in neurodevelopmental disorders. Additionally, together with Prof. Ype Elgersma, she has set-up a functional genomics screen (PRiSM), to assess the pathogenicity of variants of unknown significance.

**Bianca Zardetto** is a PhD student at the Leiden University Medical Center, and she is a member of the Dutch Center for RNA Therapeutics. Her research is focused on the development of personalised splice-modulating antisense oligonucleotide treatments for rare neurodevelopmental disorders. Her work also aims at establishing a fibroblast- and iPSC (induced pluripotent stem cell)- derived neuronal platform to facilitate treatment development and investigate the pathology of NDDs.

# Meet our chairs, 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.

**Sofia Douzgou Houge** is a clinical geneticist with an MSc in telemedicine and a PhD in dysmorphology from Hellas. She completed her specialty training in Italy, later led the Developmental Disorders team at the Manchester Centre for Genomic Medicine, UK and was awarded the FRCP. She is Editor-in-Chief of Clinical Dysmorphology and member of the Board of ERN-ITHACA, the Education Committee of the ESHG, the Advisory Committee of the Myhre Syndrome Foundation, the Board of the Manchester Rare Disease Charity, and the Board of the Norwegian Society of Medical Genetics.

**Agnies Van Eeghen**, is an Intellectual Disability Physician and provides clinical care for children and adults with genetic neurodevelopmental disorders and/or intellectual disability. She leads a research group focusing on (methodology for) interventions and personalized outcome measures, as well as neuropsychiatric trajectories over life including dementia. Additionally, she is chair of the ERN ITHACA Guideline Working Group.

**Hilde Van Esch** is a paediatrician and clinical geneticist from training and staff member at the Centre for Human Genetics at the University Hospitals UZ Leuven, where she covers a broad field of medical genetics, with specific interest in intellectual disability, neurology and syndromology as assistant Professor at KU Leuven, she heads the Laboratory for the Genetics of Cognition. Her research is focused on neurodevelopmental disorders and congenital brain malformations

**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.



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**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.

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

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

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**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.



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**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.*

***EuroNDD Scientific Committee's Chairs***

*Prof. Tjitske Kleefstra, Erasmus UMC and Radboud UMC, Center of Excellence for Neuropsychiatry at Vincent van Gogh,*
*Prof. Christiane Zweier, Universitätsspital Inselspital Bern*

***EuroNDD Organising Committee***

*Dr Laura de Graaff-Herder, Erasmus MC Rotterdam*
*Dr Marco Tartiglia, IRCCS Ospedale Pediatrico Bambino Gesù Rome*
*Prof. Zeynep Tümer, Department of Clinical Genetics, Kennedy Center, Copenhagen University Hospital – Rigshospitalet*
*ERN-ITHACA Team: Jolanda Van Golde, Anne Hugon, Marianne Le Dref, Klea Vyshka,*
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