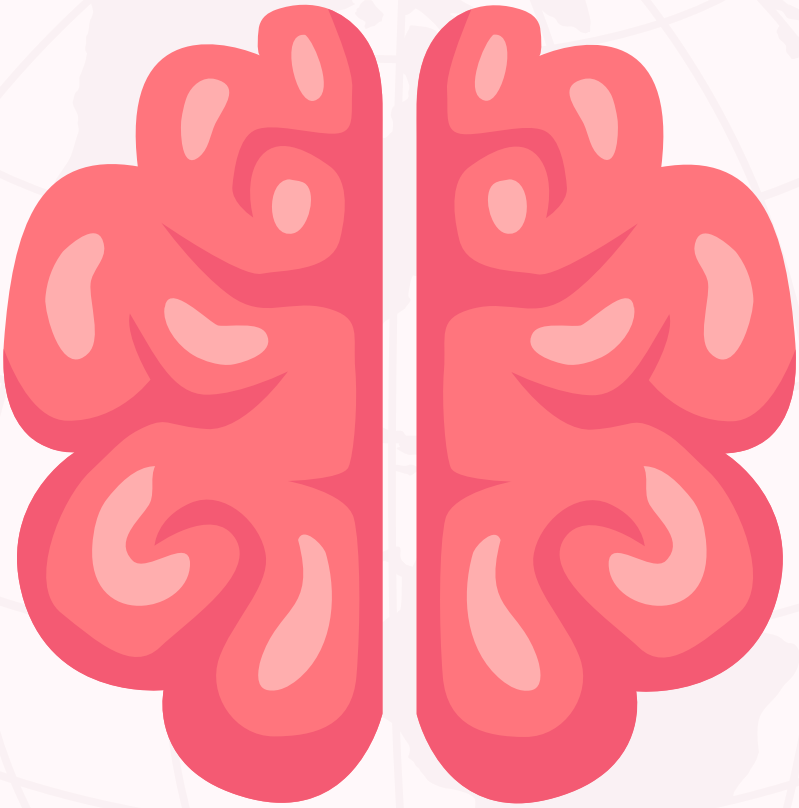
Center of Medical Genetics (UZA/UA)
Prof. dr. em. R. Frank Kooy & Dr. Claudio Peter D'Incal
with support of the European ADNP association (ADNP Europe)

Third Conference on ADNP-related and other Neurodevelopmental Disorders



9-11 September, 2026

This meeting will bring together scientists and clinicians working on the identification, characterisation, and development of treatments for genetic disorders. On **9–10 September**, we will welcome a series of internationally renowned speakers presenting the latest research on various aspects of the ***ADNP*** gene and the associated disorder, **Helsmoortel–Van der Aa syndrome**. The programme will also include short oral presentations selected from submitted abstracts on any aspect of neurodevelopmental disorders. On **11 September**, the conference will conclude with a parent and family community day for individuals with ADNP-related Helsmoortel–Van der Aa syndrome, their families and caregivers

For further information, please visit: www.uantwerpen.be/adnp-conference

CONFERENCE PROGRAMME

Wednesday, September 09, 2026

09:00 – 09:45 Registration
Location: University of Antwerp, Grauwzusters Klooster, Lange Sint-Annastraat 7, 2000 Antwerp

09:45 – 10:00 Welcome by the organising committee

Morning session, chair: Claudio D'Incal

10:00 – 10:30 Dr. Claudio Peter D'Incal (UZA/UA)
The Female Side of Autism: Sexual Dichotomies impacting the Helsmoortel-Van der Aa syndrome pathology

10:30 – 11:00 Prof. Dr. Illana Gozes (Chair Exonavis Therapeutics, LTD)
ADNP is associated with sex differences

11:00 – 11:30 **Coffee break**

11:30 – 11:45 *Short communication*: Israel Moalem
The ADNP-derived investigational drug davunetide (NAP) prevents premature death and restores neuronal proteostasis in a mouse model of Dravet syndrome

CONFERENCE PROGRAMME

Wednesday, September 09, 2026

11:45
12:00

Short communication: Lusine Harutyunyan
Expanding Clinical and Molecular Landscape of Helsmoortel-Van der Aa Syndrome

12:00
12:30

Prof. Dr. Emanuela Pascuito (VIB/UA)
Immunological aspects of ADNP

12:30
13:30

Lunch

Afternoon session, chair: Frank Kooy

13:30
14:00

Prof. Dr. Albert Basson (University of Exeter)
KDM5B neurodevelopmental disorders: mechanisms and potential therapies

14:00
14:15

Short communication: Dr. Marcus Kaji
Targeted KCNQ2 Knockdown Restores Electrical Network Development in KCNQ2 Gain-of-Function Neurons

14:15
14:30

Short communication: Dr. Mathijs Van der Lei
Bi-allelic GAD2 variants cause a rare developmental encephalopathy with early-onset seizures

CONFERENCE PROGRAMME

Wednesday, September 09, 2026

14:30 15:00	**Tea break**
15:00 15:30	Prof. Dr. David Segal (UCDavis Health) RNA therapy for Helsmoortel-Van der Aa syndrome
15:30 16:00	Prof. Dr. Zhen Yan (University at Buffalo) Pathophysiological Mechanism of ADNP Deficiency in Autism and Treatment Strategies
16:00 16:30	Prof. Dr. Joseph Buxbaum (Mount Sinai) Small-Molecule Targeting of mRNA as a Disease-Modifying Treatment for Helsmoortel-Van der Aa Syndrome

CONFERENCE PROGRAMME

Thursday, September 10, 2026

09:00 – 09:30 — Registration
Location: University of Antwerp, Grauwzusters Klooster, Lange Sint-Annastraat 7, 2000 Antwerp

Morning session, chair: Marc Bühler

09:30 – 10:00 — Prof. Dr. Hans van Bokhoven (Radboud UMC)
Multimodal mapping of neuronal network activity and multiomic convergence in neurodevelopmental disorders

10:00 – 10:30 — Prof. Dr. Giuseppe Testa (Human Technopole)
Disruption of ADNP-KDM1A-GTF2I complex drives neural differentiation imbalance in Helsmoortel-Van der Aa syndrome

10:30 – 11:00 — **Coffee break**

11:00 – 11:30 — Prof. Dr. Raymond Poot (Erasmus MC)
The ADNP protein interaction network

11:30 – 11:45 — *Short communication*: Dr. Dimitra Sokolova (VIB/UA)
Astrocyte-Derived Synaptogenic Factors Are Disrupted in an ADNP Model of Autism Spectrum Disorder

CONFERENCE PROGRAMME

Thursday, September 10, 2026

11:45 12:00	*Short communication*: Prof. Dr. Tommas Ellender (University of Antwerp) Transient prenatal exposure to NMDAR NR1 IgG has an extended impact on postnatal striatal structure and function
12:00 13:30	**Lunch**
	Afternoon session, chair: Hans van Bokhoven
13:30 14:00	Prof. Dr. Pierre Mattar (University of Ottawa) A role of ADNP in balancing gene regulation during neurodevelopment
14:00 14:30	Prof. Dr. Brian Hendrich (University of Exeter) Chromatin remodelling by CHD4 and ADNP controls gene expression at a distance
14:30 14:45	*Short communication*: Ayu Scott (UZA/UA) Functional and molecular investigation of variants in the chromatin-associated factor ADNP2
14:45 15:15	**Tea break**

CONFERENCE PROGRAMME

Thursday, September 10, 2026

15:15
15:45

Prof. Dr. Marc Bühler (FMI, Switzerland)
ADNP in command: ChAHP and genome regulation

15:45
16:00

Short communication: Nazerke Atinbayeva
Molecular characterization of a patient-specific ADNP mutation

16:00
16:30

Prof. Dr. Maarten Dhaenens (UGent)
Focus on the edges: creating easily accessible biomolecular networks of histone PTMs, metabolites and proteins to investigate ADNP functional entanglement

18:30
20:30

Reception at "Wolf" for parents and scientists, sponsored by ADNP Europe
Location: Godefriduskaai 30, 2000 Antwerp

CONFERENCE PROGRAMME

Friday, September 11, 2026

08:30 – 09:30 — Registration
Location: University of Antwerp, Grauwzusters Klooster, Lange Sint-Annastraat 7, 2000 Antwerp

Afternoon session
chairs: Kelly Verbruggen & Frank Kooy

09:30 – 09:45 — Kelly Verbruggen (ADNP Europe)
Welcome to the families and introduction

09:45 – 10:15 — Antoine Bourgoignie (ADNP Europe)
What can the ADNP European Association mean for you?

10:15 – 10:45 — Dr. Claudio Peter D'Incal (UZA/UA)
Update on the clinical presentation of the Helsmoortel-Van der Aa syndrome & sexual differences in *Adnp* frameshift mice

10:45 – 11:00 — Lusine Harutyunyan (UZA/UA)
Update on the Helsmoortel-Van der Aa syndrome care pathway and ongoing clinical studies

11:00 – 11:30 — **Coffee break**

CONFERENCE PROGRAMME

Friday, September 11, 2026

11:30 12:00	Jolijn Verseput (Radboud UMC) Natural history for Helsmoortel Van der Aa syndrome and 3D facial imaging for ADNP
12:00 12:30	Prof. Dr. Michelina Armando (Bambino Gesù Children's Hospital) Physiotherapy for the Helsmoortel-Van der Aa syndrome
12:30 13:30	**Lunch**
	Afternoon session chairs: Antoine Bourgoignie & Claudio D'Incal
13:30 13:45	ADNP Network of Hope (USA) A message from the Network of Hope
13:45 14:15	Prof. Dr. Joseph Buxbaum (Mount Sinai) Prospects for therapy in the Helsmoortel-Van der Aa syndrome
14:15 14:30	Prof. Dr. Illana Gozes (Chair Exonavis Therapeutics, LTD) Update on the Davunetide clinical trial

CONFERENCE PROGRAMME

Friday, September 11, 2026

14:30 15:00	**Tea break**
15:00 15:30	Susann Simensen (Norwegian Centre for Rare Diseases – Unit Frambu) A Holistic and Multidisciplinary Approach to Rare Disorders
15:30 16:00	A parent testimony
16:00 17:00	**Q&A session with the ADNP Europe Scientific Board Members**
17:00 19:00	**Closing reception**

Accreditation asked

ABSTRACT BOOKLET

The ADNP-derived investigational drug davunetide (NAP) prevents premature death and restores neuronal proteostasis in a mouse model of Dravet syndrome

Israel Moalem, Shaked Turk, Karni Vilian, Summer Pitocchelli, Marina Brusel, Eyal Artzy, Inbar Ben Horin-Hazak, Moran Rubinstein*, and Illana Gozes*

Department of Human Genetics and Computational Medicine, Gray Faculty of Medical & Health Sciences, Goldschleger Eye Research Institute

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*Co-corresponding authors

Objective: Dravet syndrome (DS) is a severe developmental and epileptic encephalopathy caused primarily by loss-of-function mutations in *SCN1A*. Despite multiple anti-seizure medications, DS still presents an increased risk for sudden unexpected death in epilepsy (SUDEP), highlighting the urgent need for novel neuroprotective strategies. To this end, we evaluated here the therapeutic potential of davunetide (NAP), an investigational neuroprotective peptide derived from activity-dependent neuroprotective protein (ADNP), in a mouse model of DS.

Methods: DS mice carrying the *Scn1a*^{A1783V} mutation on a pure C57BL/6J background were treated daily with davunetide (2-4 µg, subcutaneous) on postnatal days P10-P35. Survival, heat-induced seizures, growth, and behavioral phenotypes were assessed and hippocampal proteomic analysis was performed to investigate underlying mechanisms governing the therapeutic effect.

Results: Chronic davunetide (NAP) treatment prevented premature mortality in DS mice and reduced the susceptibility to heat-induced seizures. Treated mice also showed improved growth, reflected by increased body weight and length. Behavioral effects were partial, with modest improvement in social functions. Proteomic analysis identified normalization of proteins involved in microtubule dynamics, intracellular transport, mitochondrial function, autophagy, vesicle trafficking, and synaptic organization. Pathway enrichment analyses revealed convergence on cytoskeleton-dependent transport and neuronal proteostasis pathways, while Mammalian Phenotype Ontology analysis linked the corrected proteins to abnormal survival and nervous system dysfunction.

Significance: These findings demonstrate a significant therapeutic effect for davunetide (NAP) in DS mice. Beyond partial seizure protection, davunetide restored multiple interconnected pathways involved in neuronal structural homeostasis, supporting microtubule-dependent proteostasis as a therapeutic target in DS. Given its favorable clinical safety profile, davunetide (NAP) presents a promising add-on therapy to reduce the unmet need of SUDEP in DS.

Acknowledgement: This work is submitted for publication. Professor Illana Gozes serves as the VP for Drug Development at ExoNavis Therapeutics Ltd developing davunetide

ABSTRACT BOOKLET

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

Lusine Harutyunyan [1,2], Claudio Peter D'Incal [1,3], Anna C. Jansen [3,4], Marije Meuwissen [1,3], Anke Van Dijck [2] and R. Frank Kooy [1]

[1]Cognitive Genetics (COGNET), Center of Medical Genetics, Department of Medicine and Health Sciences, University of Antwerp/University Hospital Antwerp, Antwerp, Belgium.
[2]Family Medicine and Population Health (FAMPOP), Department of Medicine and Health Sciences, Translational Neurosciences (TNW), University of Antwerp, Antwerp, Belgium
[3]Genetic Epilepsies and Neurodevelopmental Disorders Research Antwerp (GENERAte), Department of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium.
[4]Division of Pediatric Neurology, Departments of Pediatrics, Antwerp University Hospital, Belgium.

Background: Helsmoortel-Van der Aa syndrome (HVDAS) is a rare multisystemic neurodevelopmental disorder caused by pathogenic variants in the *ADNP* gene. Since the first large clinical cohort was described in 2019, many additional individuals with HVDAS have been reported. However, the clinical and molecular findings from these studies have not yet been systematically synthesized.

Methods: We conducted a systematic review in accordance with PRISMA 2020, including all published individuals with genetically confirmed HVDAS. We systematically extracted clinical features, comorbidities, developmental milestones, and molecular findings, with a particular focus on newly reported and underrecognized features.

Results: We identified 105 individuals across 34 publications. Of these, 66 had both clinical and genetic data available, while 39 were reported at the genetic level only.

Our review further expands and refines the phenotypic spectrum of HVDAS, confirming the multisystemic nature of the disorder and providing additional insights into developmental delay, visual and ophthalmological abnormalities, congenital heart defects, gait disturbances, and cognitive functioning. In parallel, advances in ADNP methylation profiling are contributing to improved diagnostic accuracy and interpretation of challenging variants.

Conclusions: This systematic review provides an updated overview of the clinical, genetic, and epigenetic spectrum of HVDAS. Our findings highlight the broad phenotypic variability of the syndrome and reinforce the importance of multidisciplinary assessment and management. The increasing phenotypic heterogeneity may reflect both improved recognition of milder features and a publication bias towards more complex or severely affected individuals.

ABSTRACT BOOKLET

Targeting KCNQ2 Developmental Encephalopathy Using High-Density MEA Drug Screening in a Patient-Derived Neuronal Model

Kaji M., Dirkx N., De Vriendt E., Weckhuysen
Applied and Translational Neurogenomics Group, VIB Center for Molecular Neurology, Vlaams Instituut voor Biotechnologie, Antwerp, Belgium

KCNQ2 encodes a subunit of the Kv7.2 voltage-gated potassium channel, which plays a crucial role in regulating the resting membrane potential and modulating neuronal firing rates. These channels play an important role in neurodevelopment and neuronal excitability. Pathogenic variants in KCNQ2 cause a wide range of neurodevelopmental and epileptic disorders, including severe Developmental and Epileptic Encephalopathy (DEE) loss-of-function associated with dominant-negative (DN) mutations, and Gain-of-function (GOF) variants which lead to developmental delay with or without later-onset seizures. Currently, there is no targeted treatment and seizure control is achieved with mixed success using general antiseizure medication. No treatment options exist for KCNQ2-GOF.

To screen compounds targeting Kv7.2 channels in a therapeutically relevant cell model, our lab has developed patient-derived human induced pluripotent stem cell (hPSC) lines from individuals with KCNQ2-DN and KCNQ2-GOF and controls. These hPSC lines were differentiated into excitatory cortical neurons using NGN overexpression, and their electrical activity on a neuronal network level measured over time using high-density Microelectrode Arrays (HD-MEAs). KCNQ2-DN networks developed hyperexcitable phenotypes compared to controls with increases in individual neuronal spike rates and network-wide burst activity. In contrast, KCNQ2-GOF neuronal cultures showed delayed generation of synchronous network bursts and a general reduction in network activity, spikes per burst, and burst frequency compared to controls.

To evaluate the drug-screening capability of our models, we compared the gold-standard Kv7.2 channel opener retigabine with a novel retigabine derivative, compound 60, in their ability to reduce hyperexcitability in KCNQ2-DN networks. Treatment with retigabine successfully rescued some aspects of the KCNQ2-DN phenotype (IC50 = 3.7 µM), with compound 60 demonstrating roughly 10-fold greater potency (IC50 = 0.29 µM).

In conclusion, HD-MEA technology enabled the identification of KCNQ2-specific alterations in neuronal network activity, providing a platform to evaluate new therapies that successfully rescue KCNQ2-DN and KCNQ2-GOF phenotypes in vitro.

ABSTRACT BOOKLET

Bi-allelic *Gad2* variants cause a rare developmental encephalopathy with early-onset seizures

Mathijs B. van der Lei[1†], Matthias De Wachter[2†], Claudio Peter D'Incal[1,3], Ayu Scott[1,3], Elke Calus[4], Magali M.L. Van der Veken[1], Ellen Elinck[1], Kevin De Man[1], Yousra El Ouaamari[5], Anne Schepers[1], Ligia Mateiu[1], Debby Van Dam[4], An-Sofie Schoonjans[2], Emma Wakeling[6], Nour Elkhateeb[7], Laila Selim[8], Sabine M. Hölter[9], Susan Marschall[9], Helmut Fuchs[9], Valerie Gailus-Durner[9], Martin Hrabe de Angelis[9,11,12], Reza Maroofian[10], Berten Ceulemans[2], Anna C. Jansen[2,3] and R. Frank Kooy[1]

† These authors contributed equally to this work.

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GAD67 and GAD65, encoded by GAD1 and GAD2, respectively, are the two isoforms of glutamic acid decarboxylase, the enzyme responsible for γ-aminobutyric acid (GABA) synthesis. Pathogenic variants in GAD1 cause a severe developmental and epileptic encephalopathy, whereas GAD2 has not previously been implicated in human disease. Here, we describe four individuals from three unrelated families with bi-allelic GAD2 loss-of-function variants presenting with early-onset epilepsy, developmental delay, mild to moderate intellectual disability and autism spectrum disorder. Seizures are most severe in early infancy, but appear to diminish with age. EEG showed preserved background activity without consistent epileptiform abnormalities, and brain MRI revealed only minimal structural changes. Functional analyses in an overexpression model demonstrated that all identified variants result in truncated protein products, consistent with a recessive loss-of-function mechanism.

To further establish causality, we characterized a GAD65 knockout (GAD65-/-) mouse model. GAD65-/- mice were viable and developed spontaneous seizures, with onset as early as four weeks and showed increased susceptibility to pentylenetetrazole induced seizures. These mice also exhibited increased locomotor activity, anxiety-like behavior, repetitive behaviors, cognitive impairments and reduced sociability. Transcriptomic profiling revealed dysregulation of metabolic and mitochondrial pathways implicated in epilepsy. Our findings firmly establish GAD2 as a disease gene implicated in developmental encephalopathy with early-onset seizures. The concordance between the clinical abnormalities and the characteristics of the knockout mouse model emphasizes the pivotal role of GAD2 in neurodevelopment and epilepsy.

ABSTRACT BOOKLET

Astrocyte-Derived Synaptogenic Factors Are Disrupted in an ADNP Model of Autism Spectrum Disorder

Dimitra Sokolova[1,2], Tuur Verreydt[1,2], Ibrahim Hamad[1,2], Marcus Kaji[1,2], Bethany Geary[3], Clara Milián Alastruey[1,2], Andrew N J McKenzie[4], Frank Kooy[5], Emanuela Pasciuto[1,2]

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[3]Medical Research Council (MRC) Protein Phosphorylation and Ubiquitylation Unit, School of Life Sciences, University of Dundee, GB

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[5]Cognitive Genetics (CONGET), Department of Biomedical Sciences, University of Antwerp, Antwerp, BE

Autism spectrum disorder (ASD) is characterised by social and sensory difficulties, repetitive behaviours, and is associated with cognitive deficits. Genetic and functional studies have linked ASD to altered synaptic function, highlighting disrupted brain connectivity during neurodevelopment. Emerging data implicates astrocytes, as key regulators of the development, support, and modulation of neuronal circuits. Glial dysfunction has been linked to ASD pathology; however, whether ASD risk genes act within glial cells to drive neuronal dysfunction remains poorly understood.

De novo mutations in activity-dependent neuroprotective protein (ADNP) are among the most common single-gene causes of ASD and underlie Helsmoortel-Van der Aa syndrome. Haploinsufficient *Adnp* mutant mouse models exhibit impaired brain connectivity, deficits in social behaviour, increased repetitive behaviours, and cognitive dysfunction. ADNP is essential for brain development, with peak expression during late embryonic development (E18.5) and early postnatal days (P5), before declining by P21. Here, we demonstrate that ADNP is highly expressed in both neurons and astrocytes at the onset of synaptogenesis (P5). Given its role as a chromatin-associated regulator of gene expression, we hypothesised that ADNP regulates the production of astrocyte-derived synaptogenic factors. Consistent with this, *Adnp* mutant primary astrocytes exhibit an altered secretome, including reduced levels of key synaptogenic molecules, resulting in a diminished capacity to support neurite outgrowth and synaptogenesis.

Collectively, these findings identify astrocytes as a key cellular target of ADNP deficiency and reveal a novel astrocyte-specific mechanism underlying ASD-associated synaptic abnormalities.

ABSTRACT BOOKLET

Transient prenatal exposure to NMDAR NR1 IgG has an extended impact on postnatalstriatal structure and function

Danijela Bataveljic 1 *, Anezka Macey-Dare 1, 2 *, Zoë van Acker 1, Sukhvir Wright 3,Norbert Goebels 4, Tommas Ellender 1, 2 †

Maternal autoantibodies against the NR1 subunit of the NMDA receptor are among the most common to arise during pregnancy, and the resultant movement disorders such as dyskinesias and sensorimotor deficits seen in affected offspring strongly point toward disrupted development of the basal ganglia. Yet almost all experimental work to date has focused on cortex and hippocampus, leaving the developing basal ganglia and striatum largely unexplored. Here we present the first investigation of how transient prenatal exposure to patient-derived monoclonal NR1-IgG shapes striatal development in mice. Using intraventricular delivery to mouse embryos, we uncover selective effects on the proliferation and migration of striatal progenitors, changes in the generation and maturation of striatal spiny projection neurons and altered corticostriatal synaptic transmission. Critically, these early cellular changes translate into lasting behavioural consequences that are observed during both the neonatal period and into adulthood. Lastly, we find that a brief, well-timed postnatal intervention can reverse many of these deficits. Together, these findings identify the striatum as a key target of prenatal NMDAR autoantibodies and point toward an early, tractable opportunity for intervention.

ABSTRACT BOOKLET

Functional and molecular investigation of variants in the chromatin-associated factor ADNP2

Ayu Scott[1,2], Claudio Peter D'Incal[1,2], Marije Meuwissen[1,2], Anna C. Jansen[2,3], R. Frank Kooy[1]

[1]Cognitive Genetics (COGNET), Center of Medical Genetics, Department of Medicine and Health Sciences, University of Antwerp/University Hospital Antwerp, Antwerp, Belgium.

[2]Genetic Epilepsies and Neurodevelopmental Disorders Research Antwerp (GENERAte), Department of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium.

[3]Division of Pediatric Neurology, Departments of Pediatrics, Antwerp University Hospital, Belgium.

Background: Homeobox genes encode DNA-binding proteins that play crucial roles in embryonic development andchromatin regulation. In particular, one conserved vertebrate-specific family of homeobox genes includes the Activity-Dependent Neuroprotective Homeobox (ADNP) family. While heterozygous *de novo ADNP* variants have found to cause a severe neurodevelopmental disorder, termed Helsmoortel-Van der Aa syndrome (OMIM: 615873), variants in its sister paralog *ADNP homeobox 2 (ADNP2)* remained undetected. ADNP2 encodes a zinc finger-containing transcription factor with a conserved nuclear localization signal (NLS) that constitutes the ChAHP2 chromatin remodeling complex by a stable interaction with Heterochromatin Protein 1 Beta (CBX1/HP1β) and Chromodomain Helicase DNA-binding Protein 4 (CDH4).

Methods: Whole-exome sequencing of undiagnosed individuals and data sharing through international collaborations, GeneMatcher, and DECIPHER resulted in the first identification of nonsense, frameshift and missense variants in the coding region of the *ADNP2* gene, although their pathogenicity remains to be determined. We therefore functionally characterized the identified variants, alongside the wild-type protein, in a HEK293T overexpression system using site-directed mutagenesis of an ADNP2-GFPSpark expression vector.

Results: Using immunocytochemistry, we could demonstrate that ADNP2 locates in defined DAPI-positive foci in the nucleus with colocalization of the heterochromatin marker HP1β. In addition, we found that specific variants disrupted the established heterochromatin colocalization, thereby showing partial mislocalization to the cytoplasm. Subsequent amino acid motif analyses predicted an additional N-terminal NLS sequence (NLS1) opposed to the predefined C-terminal NLS sequence (NLS2). To confirm the function of both sequences, we selectively mutated the core amino acids to disrupt the NLS function. Sequential site-directed mutagenesis of both NLS core sequences led to complete cytoplasmic mislocalization, indicating that ADNP2 requires two NLS sequences for nuclear import. These findings were further confirmed using the β-importin inhibitor, importazole, which redirected ADNP2 to the cytoplasm, consistent with deletions of the core NLS sequences. With an established role in chromatin regulation, we also explored altered chromatin interactions using co-immunoprecipitation (CoIP) of ADNP2 in HEK293T overexpression lysates. Here, CoIP of ADNP2 nonsense and frameshift variants showed absence of HP1β interaction, while the CHD4 interaction was preserved.

Conclusion: We described the first identified human variants in the *ADNP2* gene, revealing their functional impact on protein localization, altered expression, and perturbated chromatin interactions. The disrupted ChAHP2 interactions pave the way for methylation-based diagnostic tools, such as the EPISign test, to further investigate a possible epigenetic profile in cohort. We therefore aim to determine whether such a unique episignature could be established in guiding the interpretation of *ADNP2* variants with unclear pathogenicity.

ABSTRACT BOOKLET

Molecular Characterization of a Patient-Specific ADNP Mutation

Nazerke Atinbayeva, Jakob S. Baumgartner, Nathalie Vilain, Simon Suppinger, Fabio Mohn, Jennifer Groeli, Filippo Rijli, Marc Bühler

Activity-dependent neuroprotective protein (ADNP) is a putative transcription factor (TF) that is highly conserved in vertebrates. It is associated with neuroprotection and essential for early mouse development. Together with a chromatin remodeler (CHD4) and the well-known heterochromatin binding protein HP1, ADNP forms a complex known as the ChAHP complex.

ADNP is ubiquitously expressed in human adult tissues, and de novo mutations in the ADNP gene, which predominantly result in a truncated ADNP protein, are associated with an autism-related disorder (ASD) that is known as Helsmoortel-Van der Aa syndrome (HVDAS). It is estimated that at least 0.17% of ASD patients have an ADNP mutation, which would make ADNP one of the most frequent ASD-associated genes known to date.

It is generally assumed that *ADNP* mutations in HVDAS patients are loss-of-function mutations. However, the majority of nonsense mutations found in HVDAS patients reside in the last exon of *ADNP* mRNA and the mRNA escapes nonsense-mediated mRNA decay (NMD). Thus, it is possible that truncated ADNP protein, produced in patients, could function dominantly, exerting a dominant-negative effect. Indeed, unpublished work from the lab shows that C-terminally truncated ADNP (interacting with CHD4 but not with HP1) is more strongly enriched on chromatin than wild-type ADNP.

I will explore the combinatorial effects of homo- and heterozygosity in a conditional ADNP depletion system by both using mouse embryonic stem cells (mESCs) and a gastruloid system to recapitulate early embryonic development. By using a nonsense mutation that most frequently occurs in patients, I will determine whether the HVDAS patient-specific nonsense ADNP mutation functions a loss-of-function or dominant-negative mutation.

POSTERS

Astrocyte-Derived Synaptogenic Factors Are Disrupted in an ADNP Model of Autism Spectrum Disorder

Dimitra Sokolova[1,2], Tuur Verreydt[1,2], Ibrahim Hamad[1,2], Marcus Kaji[1,2], Bethany Geary[3], Clara Milián Alastruey[1,2], Andrew N J McKenzie[4], Frank Kooy[5], Emanuela Pasciuto[1,2]

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Autism spectrum disorder (ASD) is characterised by social and sensory difficulties, repetitive behaviours, and is associated with cognitive deficits. Genetic and functional studies have linked ASD to altered synaptic function, highlighting disrupted brain connectivity during neurodevelopment. Emerging data implicates astrocytes, as key regulators of the development, support, and modulation of neuronal circuits. Glial dysfunction has been linked to ASD pathology; however, whether ASD risk genes act within glial cells to drive neuronal dysfunction remains poorly understood.

De novo mutations in activity-dependent neuroprotective protein (ADNP) are among the most common single-gene causes of ASD and underlie Helsmoortel-Van der Aa syndrome. Haploinsufficient *Adnp* mutant mouse models exhibit impaired brain connectivity, deficits in social behaviour, increased repetitive behaviours, and cognitive dysfunction. ADNP is essential for brain development, with peak expression during late embryonic development (E18.5) and early postnatal days (P5), before declining by P21. Here, we demonstrate that ADNP is highly expressed in both neurons and astrocytes at the onset of synaptogenesis (P5). Given its role as a chromatin-associated regulator of gene expression, we hypothesised that ADNP regulates the production of astrocyte-derived synaptogenic factors. Consistent with this, *Adnp* mutant primary astrocytes exhibit an altered secretome, including reduced levels of key synaptogenic molecules, resulting in a diminished capacity to support neurite outgrowth and synaptogenesis.

Collectively, these findings identify astrocytes as a key cellular target of ADNP deficiency and reveal a novel astrocyte-specific mechanism underlying ASD-associated synaptic abnormalities.

POSTERS

CTR9-related neurodevelopmental disorder: from first description to global cohort building and integrated clinical-molecular characterisation

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CTR9-related neurodevelopmental disorder (CTR9-NDD) is a recently identified ultra-rare condition caused by heterozygous missense variants in CTR9, a key component of the Polymerase-Associated Factor 1 complex involved in transcriptional regulation and chromatin organisation. Early reports describe a core neurodevelopmental phenotype characterised by developmental delay, intellectual disability, and prominent behavioural abnormalities, including autism spectrum features, emotional dysregulation and behavioural rigidity, alongside variable multisystem involvement. However, the full behavioural spectrum, natural history and underlying molecular mechanisms remain poorly defined, and robust genotype-phenotype correlations and diagnostic biomarkers are lacking. We are establishing an international multicentre cohort study to systematically characterise CTR9-NDD. Individuals with confirmed CTR9 variants will be recruited via an international clinician and parent network. Standardised deep phenotyping will be performed using harmonised clinical data collection and structured neurodevelopmental assessment. Retrospective brain MRI data will be centrally evaluated using a predefined scoring system. AI-driven facial phenotyping will be applied to investigate the presence of a recognisable dysmorphic signature. At the molecular level, functional assays in cellular models will assess variant effects on protein behaviour, and genome-wide DNA methylation profiling will be performed to identify disease-specific methylation profile. Integrated analyses will combine clinical, imaging, functional and epigenetic data. This study is ongoing; recruitment infrastructure and international collaborations are established, enabling inclusion of a sufficiently powered ultra-rare disease cohort. Pilot analyses support feasibility of harmonised data collection and multi-modal integration. This project will define the clinical and molecular landscape of CTR9-NDD and identify potential diagnostically actionable biomarkers, including a DNA methylation profile. We aim to transform CTR9-NDD from a newly described entity into a clinically actionable disorder. We actively invite clinicians and researchers to collaborate by sharing data and biological material to accelerate discovery and improve patient care.

POSTERS

ADNP function in neural crest specification and differentiation

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Activity-dependent neuroprotective protein (ADNP) is a zinc-finger and homeodomain-containing transcription factor. Mutations in ADNP lead to Helsmoortel-Van der Aa Syndrome (ADNP syndrome) which is characterised by a wide range of phenotypes involving cardiovascular, endocrine, musculoskeletal, immune and gastrointestinal systems in ad-dition to autism spectrum disorder. ADNP interacts with the chromatin remodeller CHD4 and HP1 protein (predominantly HP1γ) to form the ChAHP complex which has been sug-gested to play a role in regulating neuronal developmental programs.

There has been increasing evidence showing the importance of ADNP in maintaining lin-eage specific gene expression particularly in neurogenesis. However, the molecular mechanisms through which ADNP contributes to cell fate commitment remain unclear. Given the broad range of phenotypes associated with HVDAS patients, we chose to investigate the role of ADNP in neural crest.

To investigate the direct role of ChAHP during formation of neural crest cells (NCCs) and differentiation of the NCCs into terminal derivatives, we used an inducible degron system to rapidly degrade ADNP and CHD4 as human induced pluripotent stem cells (iPSCs) are differentiated into NCCs in culture. We show that ADNP activity is important during neural crest induction, with depleted cells showing a failure to properly respond to changes in WNT signalling levels. This resulted in morphological changes and aberrant expression of neuronal and mesodermal genes. Despite this impaired regulation, ADNP depleted iPSCs were able to form Pax3+ NCCs with reduced efficiency.

We further show that ADNP is important for NCCs to terminally differentiate into smooth muscle cells. ADNP-depleted NCC-derived smooth muscle cells show reduced proliferation and changes in cellular morphology, including a reduction in characteristic contractile phenotype of smooth muscles. We are currently investigating the molecular mechanisms driving these defects in order understand how ADNP orchestrates normal development across a diverse range of tissues.

POSTERS

Exploring the role of T cells in autism with a model of Helsmoortel-van der Aa syndrome

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Loss-function mutations in the *ADNP* gene are linked to the Helsmoortel-Van der Aa Syndrome (HVDAS), a complex neurological disorder characterized by autism and intellectual disability. Adnp mutant mice recapitulate key hallmark of ASD including learning deficit, increased anxiety and repetitive behavior. ADNP is involved in brain development, neuroprotection and modulation of the immune system. Despite a clear link exists between ADNP and the immune system, to date the exact role of ADNP in immune cell is unknown, and we ignore the contribution of the immune system to the progression or severity of the HVDAS. By improving our understanding of the link between immune and neurological dysfunction associated with ADNP deficiency, we aim to uncover underlying pathological processes and identify biological markers that enable early diagnosis and treatment of ASD.

We developed a flow cytometry based assay to measure *ADNP* expression in murine immune cells and integrated this into our high-dimensional spectral immune phenotyping platform (>40 parameters). This approach enabled the identification of both adaptive and innate immune cell subsets and allowed us to quantify *ADNP* expression at single cell resolution.

We analysed ADNP expression across multiple tissues, including spleen, thymus, and brain, at different developmental stages. ADNP expression was found to peak during early development. As expected, ADNP is highly expressed in the brain, particularly in neurons, but substantial expression was also observed in the periphery. The highest ADNP expression was detected in specific T cell subsets in the thymus, suggesting a potential role for ADNP in T cell differentiation. To further assess the functional relevance of ADNP in T cells, and to determine whether ADNP-deficient T cells contribute to the autistic-like phenotype observed in HVDAS, we crossed the ADNP floxed mouse model with a T cell specific Cre driver (Lck-Cre) and confirmed efficient T cell specific deletion.

Ongoing characterization of this model will provide critical insights into the role of ADNP in T cells and its contribution to the pathophysiology of HVDAS.

POSTERS

Defining Mutation-Specific Mechanisms of ADNP Syndrome in Human Neurodevelopment

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ADNP (activity-dependent neuroprotective protein) is a multifunctional chromatin regulator that interacts with CHD4 and HP1 to form the ChAHP complex, a protein complex that regulates gene expression and mediates DNA binding. These functions are primarily derived from mouse embryonic cells and immortalized cell lines, leaving ADNP function and pathogenic truncation effects largely unknown in human neurodevelopment. Mutations within ADNP may lead to ADNP syndrome, a severe neurodevelopmental disorder, in which most pathogenic mutations occur in the terminal coding exon, therefore escaping nonsense mediated decay and producing a truncated protein. Clinical epigenomic studies have stratified pathogenic ADNP variants into two classes: Class I mutations display a widespread hypomethylation profile while Class II mutations show focal hypermethylation. Published studies show that Class I variant p.Phe114fs*47 produces a mutant transcript, but our preliminary data show no detected protein, indicating a haploinsufficient phenotype, whereas the recurrent Class II variant p.Tyr719* produces a truncated protein that enters the nucleus but may have altered protein function. The overall goal of this project is to characterize ADNP function in human neural cells and identify the mutation-specific effects of ADNP on chromatin regulation and human neurodevelopment using iPSC-derived human stem cell models. Our central hypothesis is that p.Phe114fs*47 reduces ADNP function and chromatin occupancy while p.Tyr719* will show altered nuclear function and ectopic chromatin binding, leading to dysfunctional human neurodevelopment. Here we use induced pluripotent stem cell (iPSC)-derived excitatory neurons and integrated multi-omic and electrophysiological data analyses to determine how Class I and Class II variants affect gene expression, chromatin regulation, and neuronal function. Further, we will use iPSC-derived cortical organoids to determine whether the two variant classes disrupt cortical development using single-cell multi-omic profiling and immunofluorescence to examine cell fate trajectories. Together, these studies will define the epigenetic function of ADNP in human neural cells and identify the class-specific effects of ADNP on human neurodevelopment, therefore informing mutation-specific therapeutics.

POSTERS

Next-generation mouse phenotyping reveals multifaceted drug effects in a mouse model of Fragile X Syndrome

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Rodents, particularly mice, are indispensable preclinical models for studying human disease mechanisms and evaluating therapeutic strategies because of their genetic and physiological similarity to humans. However, despite promising preclinical findings, many drug candidates ultimately fail in clinical trials. A major bottleneck lies in behavioral validation, which relies heavily on time-consuming and costly short-term, single-animal assays that inadequately capture complex social dynamics, limiting translational relevance and reproducibility.

This challenge is particularly evident in Fragile X syndrome (FXS), the most common monogenic cause of autism and inherited intellectual disability. Numerous compounds have shown efficacy in the Fmr1 KO mouse model, but these effects have not translated into clinical success. This discrepancy highlights the shortcomings of conventional short-duration behavioral paradigms and underscores the need for a more comprehensive, translatable and standardized approach to preclinical phenotyping.

To address this gap, we combined the Live Mouse Tracker (LMT) system with the MouseKing analysis pipeline to enable standardized, continuous 24h monitoring of spontaneous behavior in socially housed mouse groups. This platform quantifies more than 35 behavioral measures aggregated into five functional domains of spatial positioning, physical social contact, motor behavior & body posture, initiation & approach and grouping & withdrawal.

Using a longitudinal, fully standardized design, we evaluated five mechanistically distinct compounds previously reported to ameliorate FXS-related phenotypes in the Fmr1 KO model. Mice underwent 24h LMT recordings at baseline, low dose, high dose, and after washout, with 14-day intervals between conditions, followed by bulk RNA sequencing after behavioral assessment. This next-generation phenotyping approach revealed that drug-induced behavioral modulation is strongly dose-dependent, rarely genotype-selective and frequently accompanied by substantial effects in WT controls.

Together, these findings establish the LMT–MouseKing platform as a rigorous and scalable framework for preclinical behavioral drug evaluation, enhancing the translational interpretability of candidate therapeutics for FXS and related neurodevelopmental disorders.

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