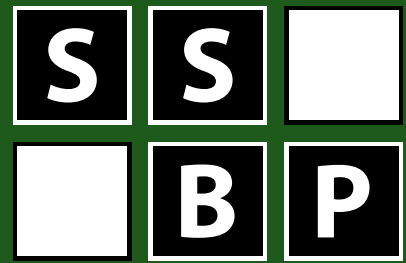


27th SSBP International Research Symposium

Programme Book

4th - 6th September 2025, Amsterdam, the Netherlands



Save the date!

28th SSBP International Research Symposium
will be held in Edinburgh, UK
3rd - 5th September 2026

Abstract submission opens: March 2026

Registration opens: April 2026

Deadline for online abstract submission: 16th May 2026

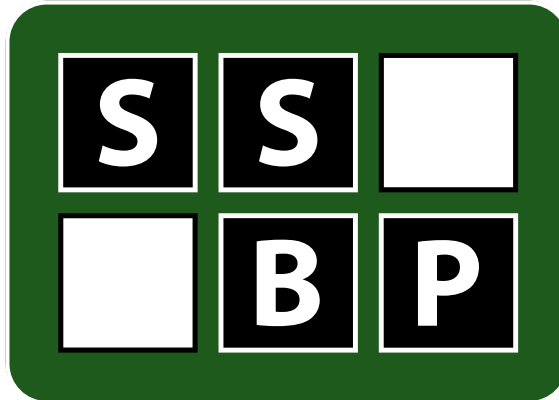
Deadline for discounted earlybird registration: 31st July 2026

Educational Day: 3rd September 2026

Research Symposium: 4th - 5th September 2026

Join us in Edinburgh, UK for our 28th research symposium.
The theme will be: *Translational Synergies: Bridging Fundamental Science
and Clinical Research in Genetic Neurodevelopmental Conditions*

See www.ssbp.org.uk for further information
and details on how to submit an abstract for an oral or poster presentation



The Society for the Study
of Behavioural Phenotypes

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4th - 6th September 2025

The 27th SSBP International Research Symposium

Amsterdam, the Netherlands

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4th - 6th September 2025

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Welcome from the Conference Organisers

With great enthusiasm we welcome you to the 27th Society for the Study of Behavioural Phenotypes International Research Symposium and Educational Day, held in Amsterdam, the Netherlands.

This year's theme, "Towards Personalised Care for Rare Genetic Disorders", focuses on the rapid developments in the field of personalised care for individuals with rare genetic neurodevelopmental disorders. It covers innovations from diagnostics and translational research to a deeper understanding of phenotypic trajectories and outcomes and contextual factors, as well as appropriate methodologies to take all of these into account. In this way, we aim to connect issues that truly matter to patients and their families, to the development of evidence-based and relevant treatments and support.

We are very pleased that speakers will address this theme from various angles, addressing both positive developments as well as the challenges that remain. A record number of high-quality abstracts has been submitted, and we have secured excellent keynote speakers for both the Educational Day and the Research Symposium. We hope you are as amazed as we are about the endeavours being made and the meaningful progress achieved in improving the quality of life for individuals with a genetic syndrome!

We encourage everyone to (re)discover Amsterdam whether it's your first visit or you're already familiar here. It's a charming, accessible and above all festive city where you'll quickly feel at home. There is so much to explore, from canals, architecture, to rich culture. And you will be able to help us celebrate Amsterdam's 750th anniversary!

We thank you for coming and hope you enjoy the meeting!

Erik Boot and Agnies van Eeghen

Conference Coordinators

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Conference Organisers

Dr. Erik Boot

Dr. Erik Boot is a physician specialized in intellectual disability medicine at 's Heeren Loo, Amersfoort, The Netherlands, and is an honorary clinical researcher at Maastricht University, The Netherlands and the University Health Network, Toronto, Ontario, Canada. He works at the multidisciplinary clinics for adults with 22q11.2 deletion syndrome and for children and adults with Smith-Magenis syndrome at 's Heeren Loo, both as a clinician and researcher. Erik Boot is a member of the scientific advisory committee of the Dutch 22q11.2 family network (Stichting Steun 22Q11) and a trustee of the 22q11.2 Society.



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Much of his research is dedicated to understanding the clinical manifestations associated with 22q11.2 deletion syndrome and enhancing the quality of life for affected adults. He was a lead author of the revised international clinical practice recommendations for the management of children and adults with 22q11.2 deletion syndrome, published in 2023. In addition, his research has focused on Smith-Magenis syndrome, the dopamine system, and parkinsonism and other movement disorders in genetic neurodevelopmental disorders.

Dr. Agnies van Eeghen

Agnies van Eeghen is an intellectual disability (ID) physician, a novel medical specialty in the Netherlands. She works at the Amsterdam UMC and 's Heeren Loo, specializing in care for individuals with and genetic neurodevelopmental disorders over the lifespan. Clinically, her focus is on Tuberous Sclerosis Complex, Fragile X syndrome, Down syndrome, and obesity syndromes.



She leads a research group 'care4rare' with 2 postdocs and 6 PhDs, including research on neuropsychiatric trajectories, (biomarkers for) ageing, clinical trials for neuropsychiatric manifestations such as CBD oil and SSRIs, and development of relevant and personalized outcome measures and core outcome sets. All pertaining to rare genetic neurodevelopmental disorders.

She chairs the the European Reference Network ITHACA guideline working group, developing syndrome-specific guidelines as well as on overarching themes such as transition of care, and adapting methodology to the respective patient populations. Also, she is involved in the working groups of various other (inter)national guidelines.

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Scientific Committee

Dr Erik Boot

Senior Researcher,

's Heeren Loo, Amersfoort, the Netherlands

Maastricht University, the Netherlands

University Health Network, Toronto, Ontario, Canada

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Prof Petrus J de Vries

Struengmann Professor of Child & Adolescent Psychiatry,

University of Cape Town, South Africa

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Medical Director of Child and Youth Community Health Services & Child Development Medical Lead,

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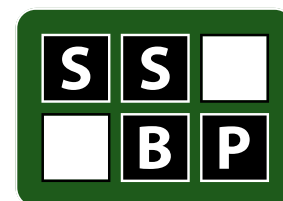
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The SSBP



The **Society for the Study of Behavioural Phenotypes (SSBP)** is an international, interdisciplinary research society for studying the development, learning and behaviours of individuals with genetic disorders and ways of helping to improve lives. The society is registered as a charity in the UK (No. 1013849) and was set up in 1987 with four main goals:

1. To promote and facilitate research into the causes, clinical features and treatment of 'behavioural phenotypes' (the characteristic learning and behavioural patterns associated with specific genetic syndromes)
2. To encourage collaboration and communication between clinicians and researchers in studying behavioural phenotypes
3. To raise awareness and promote education about behavioural phenotypes in the scientific and clinical communities and the general public
4. To strive for the highest ethical standards in research and clinical practice involving children and adults who have learning and behavioural problems associated with genetic disorders

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Meetings of the SSBP

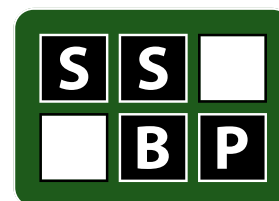
Year	Location	Meeting
1991	Kings Fund, London, UK	Workshop
1992	Welshpool, UK	2 nd International
1993	Royal Society of Medicine, London, UK	4 th Annual
1994	Maastricht, the Netherlands	3 rd International
1995	Edinburgh, UK	6 th Annual
1996	Dublin, Ireland	4 th International
1997	Cambridge, UK	7 th Annual
1998	Baltimore, USA	5 th International
1999	Birmingham, UK	8 th Annual
2000	Venice, Italy	6 th International
2001	Oxford, UK	9 th Annual
2002	Whistler, Canada	7 th Scientific
2003	Newcastle, UK	10 th Annual
2004	Barcelona, Spain	8 th International
2005	Cairns, Australia	9 th International
2006	Dublin, Ireland	11 th Annual
2007	MIND Institute, Sacramento & Lake Tahoe, USA	10 th International
2008	Cologne, Germany	11 th International
2009	Cambridge, UK	12 th International
2010	Pavia, Italy	13 th International
2011	Brisbane, Australia	14 th International

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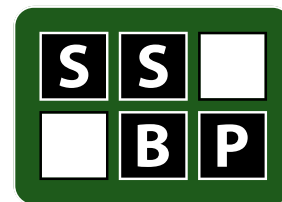
SYNDROMES



Year	Location	Meeting
2012	Leuven, Belgium	15 th International
2013	Stellenbosch, South Africa	16 th International
2014	New York, USA	17 th International
2015	London, UK	18 th International
2016	Siena, Italy	19 th International
2017	Leiden, the Netherlands	20 th International
2018	Melbourne, Australia	21 st International
2019	Birmingham, UK	22 nd International
2021	Virtual	23 rd International
2022	Oslo, Norway	24 th International
2023	Virtual	25 th International
2024	Bali, Indonesia	26 th International
2025	Amsterdam, the Netherlands	27 th International

Forthcoming Meetings of the SSBP

2026	Edinburgh, UK	28 th International
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The SSBP Executive Committee

Life President	<i>Professor Patricia Howlin</i> (UK) (patricia.howlin@kcl.ac.uk)
President	<i>Professor Petrus de Vries</i> (South Africa) (petrus.devries@uct.ac.za)
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Tom Oppé and the Tom Oppé Distinguished Lecture

Tom Oppé

Tom Ernest Oppé (1925 - 2007) was Professor of Paediatrics at St Mary's Hospital Medical School, University of London, between 1969 and 1990. Over this period he built up a large and respected department. He had a wide range of clinical and research interests, but had a particular passion for the abnormal behaviours associated with genetic syndromes.

Oppé was born in London and was educated at University College School and Guy's Hospital, qualifying with distinction in 1947. He did his national service in the Navy, where a colleague had a child with Williams syndrome. Many believe that this was where Tom's interest in behavioural phenotypes was first stimulated.

After some years at Great Ormond Street, a research fellowship at Harvard and 2 years in Bristol, he returned to St Mary's Hospital (where he had worked as Lecturer in Child Health), and stayed at St Mary's for the rest of his professional career. He was awarded a CBE in 1984 for services to paediatrics and child health.

Tom was a founder member of the SSBP in 1987 and became Life President of the Society in 2001. He died in 2007 aged 82. This lecture is dedicated to his memory in appreciation for his work for the SSBP and for children with genetic and developmental disorders.

Tom Oppé Lecturers

2025	Emily Farran
2024	Gauri Divan
2023	Mustafa Sahin
2022	Kevin Mitchell
2021	Liz Pellicano
2019	Louise Gallagher
2018	Bruce Tonge
2017	James Harris
2016	André Strydom
2015	Michael Rutter
2014	Stewart Einfeld
2013	Patricia Howlin
2012	Chris Oliver
2011	Tony Holland
2010	Randi Hagerman
2009	Alcino Silva
2008	Hans-Christoph Steinhausen
2007	Petrus J de Vries

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2025 Tom Oppé Distinguished Lecturer: Professor Emily Farran

Emily Farran is Professor of Cognitive Development, at the University of Surrey, UK, and a member of the Centre for Educational Neuroscience, University of London, UK. Emily directs the Cognition, Genes & Developmental Variability Lab. Her research relates to cognitive development, with a specific emphasis on spatial cognition. The broad aim of her research is to characterise typical and atypical development of cognitive functions within the context of the developing brain. This involves analytical investigation of spatial performance in both small-scale (e.g. perception, mental imagery) and large-scale space (navigation and route learning abilities), and the relationship between spatial thinking and Science Technology Engineering and Maths (STEM). Emily works with primary school children and individuals with genetic syndromes. Emily has published over 100 journal articles and her research has been funded by the Economic and Social Research Council, the British Academy, the Leverhulme Trust, the Nuffield Foundation, the Wellcome Trust, the Education Endowment Fund, the Waterloo Foundation, Autour des Williams, the Williams Syndrome Foundation, and Fondation Jerome Lejeune.



Patricia Howlin and the Patricia Howlin Prize Lecture



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After 9 years as Chair of the SSBP, Pat Howlin stepped down in 2008. At the 2008 Annual General Meeting (AGM). The SSBP membership recommended that a named lecture or prize be instituted in gratitude for Pat's excellent contributions to the Society. Pat was elected to the Executive Committee of the SSBP in 2013 as our Global Representative. Pat Howlin then served as President of the SSBP for 9 years and then, at the 2024 AGM, the SSBP membership voted to make her the SSBP Life President.

Pat Howlin Prize Lecture:

Area of Research:

Intervention-based research that links directly to the learning or behavioural problems of individuals with genetic syndromes and related neurodevelopmental disorders. Preference will be given to nonpharmacological interventions such as behavioural, cognitive or psychological. However, studies directly examining aspects of neurocognition and behaviour using pharmacological or medical studies will also be considered.

Eligibility of applicants:

The award is aimed at younger rather than senior and well-established researchers. The award would normally be for researchers below the level of senior lecturer/associate professor. Membership of the SSBP is a requirement.

Award Procedure:

The award was launched at the AGM in 2009. Abstract submission forms will have a box to indicate that the submitting author believes their abstract to fall within the remit of the Prize Lecture as listed above, and that they are eligible to be considered for the award.

The award will be judged by the Organising Committee of each Research Symposium who will make a recommendation to the SSBP Executive Committee at least 1 month prior to the SSBP Research Symposium. Once approved by the SSBP Executive, the successful candidate will be invited to present the Prize Lecture.

The award winner will receive free registration for the current SSBP Research Symposium along with a prize of £250 (or equivalent) and an award certificate - both of which will be presented to the winner during the SSBP Research symposium.

Patricia Howlin Lecturers

2025	Alice Federica Maria Montanaro
2023	Laura Roche
2022	The TAND Consortium
2021	Jandu Yani U Research Group
2019	Jeanne Wolstencroft
2016	Shruti Garg
2015	Supriya Malik
2014	Hayley Crawford
2013	Mary Heald
2012	Sheena Grant
2011	Leah Bull
2010	Debbie Allen

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2025 Pat Howlin Prize Winner: Alice Montanaro

Alice Montanaro is a cognitive-behavioural therapist and consultant researcher at the Center for Neurodegenerative Diseases and the Aging Brain, Department of Clinical Research in Neurology, University of Bari Aldo Moro / Pia Fondazione Cardinale G. Panico. She is currently a PhD fellow in Human Relations Science at the Department of Education, Psychology, and Communication, University of Bari Aldo Moro, with a research focus on cognitive-behavioural interventions and clinical characterization in the context of Fragile X Syndrome and FMR1 premutation. She is a licensed clinical psychologist, neuropsychologist, and cognitive-behavioral therapist, with expertise in integrative, multimodal therapeutic approaches. Her clinical work involves the application of evidence-based methods for the treatment of various mental health conditions, including anxiety disorders, depression, and learning disabilities.



Petrus de Vries and the Leclezio-de Vries Lecture



Petrus J de Vries

Petrus de Vries succeeded Patricia Howlin as Chair of the SSBP in 2008, and stepped down in 2017. At the 2018 Annual General Meeting (AGM), the SSBP membership recommended that a named lecture or prize be instituted in gratitude for Petrus' longstanding commitment and tireless work on behalf of the Society. At the 2024 AGM, the SSBP membership voted to elect Petrus to the role of SSBP President

The Leclezio-de Vries Lecture:

Area of Research:

The Leclezio-de Vries Lecture recognises work in the area of socially responsive research, with a particular emphasis on community participation. Petrus de Vries requested the lecture be in honour of Loren Leclezio, who was his first MSc and then PhD student at the University of Cape Town. She was a student member of the SSBP from 2012 and was on the organising committee of the 2013 SSBP conference in South Africa. Loren sadly died in 2018, very shortly after receiving her PhD. She was passionate about participatory research that would make a significant difference to the lives of families and communities of people living with Tuberous Sclerosis Complex or other rare diseases.

Eligibility of applicants:

Priority for the award is given to younger rather than senior and well-established researchers – this award would normally be for researchers below the level of senior lecturer/associate professor. Priority may also be given to applicants from an Low or Middle Income Country. Membership of the SSBP is a requirement.

Award Procedure:

The award was launched at the 2019 SSBP conference, with a winner selected from among the abstracts submitted. Abstract submission forms have a box to indicate that the submitting author believes their abstract to fall within the remit of the Lecture as listed above, and that they are eligible to be considered for the award.

The award is judged by the Organising Committee of each Research Symposium who make a recommendation to the SSBP Executive Committee at least 1 month prior to the SSBP Research Symposium. Once approved by the SSBP Executive, the successful candidate will be invited to present the Lecture. The award winner receives free registration for the current SSBP Research Symposium along with a prize of £250 (or equivalent) and an award certificate - both of which will be presented to the winner during the SSBP Research symposium.

The Leclezio-de Vries Lecturers

2025	Tosca-Marie Heunis
2024	Talia Thompson
2023	Jeanne Wolstencroft
2022	The TAND Consortium
2019	Ms Siobhan Blackwell

2025 Leclezio-de Vries Lecturer: Dr Tosca-Marie Heunis

Tosca has a background in the field of biomedical engineering with applications in autism and Tuberous Sclerosis Complex Associated Neuropsychiatric Disorders (TAND). Her PhD focused on the early detection of autism spectrum disorder using recurrence quantification analysis of resting state electroencephalographic (EEG) signals. She was the project coordinator and technology group lead on the TANDem-1 project, Empowering Families Through Technology, an international mobile-health project focused on developing a smartphone application to reduce the TAND identification and treatment gap. She is a member of the TAND consortium, currently the project coordinator and technology group lead of the TANDem-2 research project, and is based at the Vrije Universiteit Brussel, Belgium.



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Other SSBP Prizes and Awards

The James Harris Scholarship

Professor James C. Harris (1940 - 2021) was a longstanding and stalwart member of the SSBP, serving on the executive committee as the US East Coast representative for many years. He was awarded Honorary Membership of the SSBP, and attended many meetings of the SSBP together with his wife, Dr Cathy DeAngelis, where his contributions as an academic, colleague, mentor and photographer were truly valued.

He studied at the University of Maryland and the George Washington School of Medicine, and completed a residency and fellowship both in adult and in child & adolescent neuropsychiatry at the Johns Hopkins Medical Institution. He was later a professor and director of the Developmental Neuropsychiatry Clinic at Johns Hopkins University, where he founded the autism program. Dr. Harris's two-volume textbook, Developmental Neuropsychiatry, won the Doody's Medical Book of the Year Award in 1995.

The James Harris scholarship was created and first awarded in 2023 to support a member of the SSBP from a LMIC country to attend the SSBP meetings. Each year, the scholarship will be awarded to the author of the highest scoring abstract received from an SSBP member from an LMIC country, as scored by the scientific committee. The James Harris Scholarship will cover registration, and £250 (or equivalent) towards travel and accommodation costs.

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2025 James Harris Scholarship Winner: Prof. Dr. Dragana Protic

Prof. Dragana Protic, MD, PhD, is an associate professor of clinical pharmacology at the Faculty of Medicine, University of Belgrade, whose work has significantly advanced fragile X syndrome (FXS) research and care in Serbia and across Europe. Since collaborating with the MIND Institute at the University of California, Davis in 2018, she has shown exceptional commitment to improving the lives of individuals with FXS, the most common inherited cause of intellectual disability and autism spectrum disorders. In 2019, she organized the first national conference on FXS and related disorders in Belgrade - a landmark event uniting experts, families, and policymakers, and greatly raising awareness. Her leadership, organizational skills, and scientific expertise have helped establish Belgrade as a recognized hub for FXS research and treatment. She has built a strong clinical and scientific network addressing unmet needs, bridging gaps in diagnosis, care, and follow-up. Prof. Protic has published in leading journals, leads and participates in national and international research projects, and actively mentors young researchers while promoting high ethical standards. Her career reflects a rare integration of research excellence, clinical expertise, and compassionate advocacy, with lasting impact on both the regional and global fragile X community.



The Martin Bax Poster Prize

The Martin Bax Poster Prize is awarded for the best poster by a junior member of the SSBP. This award is given to celebrate Martin Bax, who was one of the original founders of the SSBP, served as Chairman for many years and was later President of the SSBP. The recipient of the prize is named at the meeting.

Sponsors

The SSBP is extremely grateful to the following organisations for their sponsorship of SSBP 2025 in Amsterdam.



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These sponsorships are unrestricted educational grants. The sponsors had no influence or role in programme development or speaker selection.

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Venues



Educational Day (4th September)

The Educational Day will be held at:
Amsterdam University Medical Centre.
Amsterdam UMC, Location AMC
Meibergdreef 9
1105 AZ Amsterdam



Welcome Reception (4th September)

The Conference Reception will be held at:
Groot Melkhuis
Vondelpark 2
1071 AA Amsterdam



Research Symposium (5th–6th September)

The Research Symposium will be held at:
The Royal Tropical Institute (KIT)
Mauritskade 64
1092 AD Amsterdam



Conference Dinner (5th September)

The Conference Dinner will be held at:
De Vergulden Eenhoorn
Ringdijk 58
1097 AH Amsterdam

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Keynote Speaker Profiles:

(In Alphabetical Order)

Dr Lotte Haverman

Dr. Lotte Haverman is a clinical paediatric psychologist by training and head of the research group PROMs & paediatric psychology at the Emma Children's Hospital, Amsterdam UMC. She specializes in integrating Patient-Reported Outcome Measures (PROMs) into routine clinical care (paediatric and adult care) to enhance patient-centred approaches. Dr. Haverman led the development and implementation of the KLIK PROM portal, now utilized in over 40 Dutch hospitals, facilitating systematic monitoring of Patient Reported Outcomes. Her research emphasizes patient engagement. Additionally, she focuses on developing PROMs, studying psychometrics and creating core PROM sets for vulnerable individuals (e.g. communication disabilities or genetic intellectual disabilities), aiming to standardize patient-centred outcomes in rare diseases.



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Professor Vivi Heine

Vivi Heine is full professor of Human Model Systems at the Emma Children's Hospital and board member of the Emma Center for Personalized Medicine (EmmaCPM) and Dutch Society for Human Genetics (NVHG). She studies the pathophysiology of developmental brain disorders by considering a glial component. For long research was focused on neurons, while glia dysfunction is increasingly being shown to contribute to various neurological disorders. Her research centers around induced pluripotent stem cell (iPSC) technology and disease models from patients with genetic neurodevelopmental disorders, including Tuberous Sclerosis Complex (TSC), Rett syndrome, GRIN2B, Schizophrenia, and the brain white matter disorders 4H syndrome and Adrenoleukodystrophy (ALD). Her lab optimized procedures to generate human 2D or 3D iPSC-derived neuron-glia co-cultures and organoid models that are functionally characterized by advanced microscopy, electrophysiology, proteomics and/or high content cellular screening. She performed ground studies that identified how neuron-glia interactions contribute to brain network dysfunctions in these neurodevelopmental disorders.



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Dr Mirthe Klein Haneveld

Mirthe Klein Haneveld is a medical doctor, care ethicist, and epidemiologist in training. She currently works as a PhD candidate and genetic counsellor at Amsterdam University Medical Hospitals. Her research focuses on developing clinical practice guidelines for rare genetic conditions associated with intellectual disability. She aims to address the unique methodological challenges imposed by rare diseases, while strengthening partnerships with individuals and families living with these conditions. This work is part of the European Reference Network ITHACA, which supports rare malformation syndromes and neurodevelopmental disorders.



Professor Therese van Amelsvoort

Therese van Amelsvoort is professor of Transitional Psychiatry and consultant Psychiatrist at Maastricht UMC. After finishing her medical studies in Rotterdam (1991), she worked as a medical and scientific advisor in Basel (Switzerland, 1991-1993) and as a resident in psychiatry in Luxemburg (1993-1994). Subsequently, she trained as an academic psychiatrist at The Maudsley Hospital / Institute of Psychiatry in London (UK, 1994-2001). She has had a longstanding interest in neurobiological mechanisms underlying psychosis and neurodevelopmental disorders, in particular 22q11DS. She obtained her PhD on 22q11DS in 2004 at the University of Amsterdam. Since 2012 she is working at The Department of Psychiatry and Psychology at Maastricht University Medical Centre, running the Dutch adult 22q11DS clinic and with a special focus on the transition from adolescence to adulthood in both her clinical and academic work. She is co-founder of @ease, the Dutch variant of the successful Australian Headspace, an innovative youth mental health service.



Associate Professor Peter van de Ven

Peter van de Ven is a biostatistician and associate professor of clinical trial methodology at the University Medical Center Utrecht (UMCU) where he leads the Clinical Trial Methodology & Statistical Consultation team. His research focusses on innovations in clinical trial methodology that help make trials more efficient, such as applications of Bayesian methods in trials and adaptive trials. As a statistical consultant at UMCU and Amsterdam UMC, he advised on the design and statistical analysis for trials in several rare diseases and conditions, including trials for treating behavioral manifestations in Smith-Magenis syndrome, Fragile X Syndrome and Tuberous Sclerosis Complex. He was a member of the N-of-1 for all consortium that focused on N-of-1 trials in metabolic diseases. Besides being an associate professor at UMCU, he is a seconded methodology assessor for the Dutch Medicines Evaluation Board (CBG-MEB).



Professor Marianne van den Bree



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Marianne van den Bree is a Professor of Psychological Medicine within the Division of Psychological Medicine and Clinical Neurosciences and the Neuroscience and Mental Health Innovation Institute at Cardiff University. She has a background in psychology, human genetics, and epidemiology. She studied in the Netherlands (BSc and MSc) and USA (PhD). She leads the Rare Genetic Variant Research Programme (ECHO; <https://www.cardiff.ac.uk/centre-neuropsychiatric-genetics-genomics/research/themes/developmental-psychiatry/copy-number-variant-research-group>) at Cardiff University. This longitudinal programme has recruited and assessed >3,000 children and young people with mutations linked to high risk of neurodevelopmental and psychiatric conditions as well as unaffected siblings and parents. It combines detailed and wide-ranging phenotyping throughout childhood, adolescence and adulthood with neuro-imaging, and genetic and pharmacological studies.

She also directs the Lifespan multimorbidity research Collaborative (LINC; <https://www.cardiff.ac.uk/lifespan-multimorbidity-research-collaborative/people>), an international programme investigating the role of rare and common genetic factors in the development of physical and mental health multimorbidity across the lifespan in eight longitudinal population-based cohorts (aggregate n~7M).

She is furthermore a key investigator within a number of other national and international consortia, including IMAGINE-ID (<https://imagine-id.org/>) and Genes to Mental Health (G2MH; <https://genes2mentalhealth.com/about/g2mh/>) and a member of Advisory Panels such as the Cleft Collective cohort at Bristol University.

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Prof. Mieke M. van Haelst

Prof. Mieke van Haelst was trained as a clinical genetics at Erasmus MC, Rotterdam and Great Ormond Street Hospital, London, UK. She has worked as a clinical geneticist at Guy's & St Thomas' hospital and Northwick Park hospital, London and UMC Utrecht before she started working as head of Clinical Genetics and board member of the Department of Human Genetics.



Her clinical and translational research focusses on the identification of (novel) gene defects and unravelling the pathogenicity obesity-related disorders. As co-director of Emma Center for Personalized Medicine at Amsterdam UMC, she works on the identification and understanding of causal (epi)genetic factors that result in rare diseases. She integrates knowledge and methods of diverse disciplines to accelerate the development of personal treatment for rare genetic disorders. She has established genetic clinics, research and education programs at the pediatric departments in the Dutch Caribbean and aims to provide equal genetic care for diverse populations.

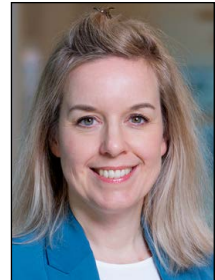
Jan-Paul Wagenaar

Jan-Paul Wagenaar is the chair of the Dutch TSC-patient advocacy group 'Stichting Tubereuze Sclerosis Nederland' (STSN). He joined the board of the STSN in 2005 and was responsible for fund raising and financial accountability. In 2013 he became chair of the STSN. In 2026 the STSN will celebrate its 45th anniversary. After decades of successful activities and fruitful cooperation with the Dutch network of TSC-experts, being involved in various research initiatives, the STSN has to reset its priorities and targets. Making the STSN, an advocacy group of a rare disease run by volunteers only, ready for the future is a real challenge. Jan-Paul has witnessed great steps forward in the diagnosis and care of TSC and the growing awareness of the importance of behavioral aspects associated with TSC. But there are still many things to be improved. Finding ways to increase the perspective of parents and caretakers to deal with the 24/7 task to improve the living quality of people with TSC is the focus of the STSN for the years to come. Jan-Paul has a son of 24 with TSC. In his day-to-day life he works in agricultural research in the Netherlands.



Dr Janneke Zinkstok

Janneke Zinkstok is a child, adolescent and adult psychiatrist, and associate clinical professor at the Radboud university medical center and at Karakter child and adolescent psychiatry Nijmegen, the Netherlands. She partially trained at the Institute of Psychiatry and Maudsley Hospital in London where she specialized in autism and ADHD in adults. Her clinical expertise is in assessment and management of mental illness in people with intellectual disabilities and genetic syndromes. Her research focuses on 1) clinical research aimed at behavioral phenotyping of specific syndromes including 22q11 deletion syndrome, Smith Magenis syndrome and Dravet syndrome; and 2) research aimed at exploring experiences and needs of patients and families, with the overall aim to empower families coping with neurodevelopmental conditions. She initiated a tool facilitating matched individual peer support for parents caring for children (of all ages) with developmental conditions in the Netherlands. She is passionate about continuously bringing patient and family perspectives to the forefront and to integrate their views with a view to organizing and delivering the best clinical care, always with a life span perspective. Her research is published in international peer reviewed journals. She firmly believes in team science and invests in mentoring and coaching students and junior doctors in her team.



Educational Day Programme

Thursday 4th September 2025 – Amsterdam UMC, location AMC

08:30 – 09:15 **Registration and coffee**

09:15 – 09:30 Welcome from the Conference Organisers

Session 1. Chair: Erik Boot

09:30 – 10:00 **KEYNOTE: 1. Jan Paul Wagenaar** - TSC – Our journey with a rare disease

10:00 – 10:45 **KEYNOTE: 2. Professor Therese van Amelsvoort** - Transition from youth to adult care, most recent insights and future challenges

10:45 – 11:15

MORNING REFRESHMENTS

Session 2. Chair: Sylvia Huisman

11:15 – 12:00 **KEYNOTE: 3. Dr. Janneke Zinkstok** - Family-oriented care for rare genetic syndromes

12:00 - 12:45 **Free Communications** - 3 x 15 minutes

4. **Jeanne Wolstencroft** - Mental health support priorities for families caring for children with rare genetic conditions

5. **Josephine Haddon** - Family Emotional climate is associated with neuropsychiatric outcomes in young people with neurodevelopmental risk genetic conditions

6. **Danielle Baribeau** - Psychopharmacology in children with genetic disorders of epigenetic and chromatin regulation

12:45 – 13:45

LUNCH

Session 3. Chair: Janneke Zinkstok

13:45 – 14:30 **KEYNOTE: 7. Professor Mieke van Haelst** - Care for Genetic Obesity – experiences from the Dutch Expert Center for Genetic Obesity

14:30 – 15:15 **Free Communications** - 3 x 15 minutes

8. **Jessica Hall** - Longitudinal development of prodromal psychosis in young people at high genomic risk of schizophrenia

9. **Ann Swillen** - The added value of using infographics on the educational and psychosocial needs of children and adolescents with 22q11 DS in school: the Leuven experience

10. **Ida Elken Sørderby** - TRICXY-MINDS: Clinical insight into sex Trisomies for enhanced psychiatric Care in individuals with X and Y chromosomal aneuploidies in Norway

15:15 – 15:45

AFTERNOON REFRESHMENTS

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Session 4. Chair: Andrew Stanfield

15:45 – 16:15 **KEYNOTE: 11.** Dr. Mirthe Klein Haneveld - Clinical practice guidelines for rare genetic conditions associated with intellectual disability

16:15 – 16:45 **Free Communications** - 2 x 15 minutes

12. Nicole Tartaglia - Exploring the Role of Parental Cognitive Skills on 36-month Outcomes in Children with Prenatally Diagnosed XXY, XYY, and Trisomy X

13. Kayla Smith - Advancing detection of social anxiety in fragile X syndrome: A multi-method exploration of social behaviour, heart activity, and heart rate-defined sustained attention

16:45 Close of Educational Day

18:30 – 20:30

CONFERENCE WELCOME RECEPTION
– Welcome Reception at Groot Melkhuis, Vondelpark
Drinks and canapes are provided, Pizza is available to order

Research Symposium Programme

Day 1

Friday 5th September 2025 – KIT Institute

08:15 – 08:45 **Registration (for new arrivals) and poster set-up**

08:45 – 09:00 Welcome from the Conference Organisers

Session 5. Honey Heussler / Pat Howlin

09:00 – 09:45 **KEYNOTE: 14. Professor Emily Farran – Tom Oppé Distinguished Lecture**

- What are the gaps in research for the communities of people with Down Syndrome, Fragile X Syndrome and Williams Syndrome?

09:45 – 10:30 **Free Communications** - 3 x 15 minutes

15. Alice Federica Maria Montanaro – **The Pat Howlin Prize** - Cognitive behavioural therapy in adolescents with Fragile X Syndrome: a feasibility randomized controlled trial

16. Flora Tassone - Molecular, Neurocognitive and Psychosis Risk Profiles in Youth and Young Adults with 22q11.2 Deletion Syndrome: Longitudinal Findings from a Multimodal Study

17. Sarah Eley - Gene therapy in Fragile X Syndrome: A caregiver perspective

10:30 – 11:00

MORNING REFRESHMENTS

Session 6. Chair: Audrey Thurm

11:00 – 11:45 **KEYNOTE: 18. Dr. Peter van de Ven** - Statistical challenges of trials in rare genetic disorders

11:45 – 12:15 **Speed Communications** - 6 x 5 minutes

19. Kaat Theelen - Development and validation of the Klinefelter-Associated Neurodevelopmental Difficulties (KAND) Checklist: a three-phase mixed-methods study

20. Alannah Hijlkema - PROM4RARE: the final core patient reported outcome set for individuals with genetic intellectual disability

21. Floortje Hosman - COS4TAND: Towards a Core Outcome (Measure) Set for TSC-Associated Neuropsychiatric Disorders (TAND)

22. Aaron Kaat - Concept Formation as a Cognitive Outcome Measure in Rare Diseases

23. Lindsey Mizen - Using machine learning to explore behavioural phenotypes across single gene neurodevelopmental conditions

24. Maarten Otter - Social functioning as a predictor of development in adult women with triple X syndrome

12:15 – 12:30

Combined Q&A

12:30 – 13:45

LUNCH & POSTER VIEWING

Session 7. Chair: Jane Waite	
13:45 – 14:30	KEYNOTE: 25. Dr. Lotte Haverman - Bridging the Gap: Developing a Generic PRO Set for Individuals with (Genetic) Intellectual Disabilities
14:30 – 15:00	Free Communications - 2 x 15 minutes
	26. Sara Jane Webb - Factors that impact short and medium term stability on clinical trial measures in children with autism
	27. Jane Waite - Psychometric Properties of the Clinical Anxiety Screen for People with Severe to Profound Intellectual Disabilities and its Application to Cross-Syndrome Research
AFTERNOON REFRESHMENTS	
Session 8. Chair: Petrus de Vries	
15:30 – 16:00	Free Communications - 2 x 15 minutes
	28. Sydni Weissgold - An investigation of autonomic function in SYNGAP1-related Intellectual Disability
	29. Tosca-Marie Heunis – Leclezio-de Vries Prize Lecture Prize Lecture - Feasibility and Acceptability of the TAND Toolkit App
16:00 – 16:30	Panel discussion
16:30	Closure of day 1
18:00 for 18:30	CONFERENCE DINNER – at Vergulden Eenhoorn

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Research Symposium Programme

Day 2

Saturday 6th September 2025 – KIT Institute

Session 9. Chair: Randi Hagerman

09:00 – 09:40 **KEYNOTE: 31. Vivi Heine** - Human iPSC-Based Disease Models for Personalized Therapeutics in Neurodevelopmental Disorders

09:45 – 10:30 **Free Communications** - 3 x 15 minutes

32. **Shanlee Davis** - Impact of Infant Testosterone Treatment on Neurodevelopment in Boys with 47,XXY

33. **Randi Hagerman** - Controlled Trial of Metformin in Fragile X Syndrome

34. **André Strydom** - Evaluation of the effect of intranasal insulin on development and behaviour in PhelanMcDermid syndrome

10:30 – 11:00

MORNING REFRESHMENTS

Session 10. Chair: Flora Tassone

11:00 – 11:45 **Free Communications** - 3 x 15 minutes

35. **Hilgo Bruining** - Bridging Genetic Bridges: Unravelling E/I Imbalance to Unlock Personalized Treatments in Monogenetic Disorders

36. **David Owen** - Proteomic profiles related to neurodevelopmental copy number variant carriers in UK Biobank open new insights into internalising and cardiometabolic multimorbidity

37. **Riccardo Brambilla** - p70 S6 kinase as a potential peripheral biomarker for 16p11.2 copy number variant- associated neurodevelopmental syndromes

11:45 – 12:10 **Speed Communications** - 5 x 5 minutes

38. **Yiting Zhu** - Effects of metformin versus placebo on children with fragile X syndrome: a randomized, double-blind, placebo-controlled clinical trial

39. **Mana Nasori** -Parents' and healthcare professionals' experiences in interprofessional collaboration in rare genetic intellectual disability syndrome: A qualitative study into barriers and facilitators

40. **Darren Hocking** - Elucidating interactions between attentional control and socially oriented attention in young children with neurofibromatosis type 1

41. **Damien Wright** - Resting state EEG power and connectivity in SYNGAP1-related disorder

42. **Danyong Feng** - Age-Varying Distinct Neuroanatomy in Young Children with Autism Spectrum Disorder and Fragile X Syndrome

12:10 – 12:20

Combined Q&A

12:20 – 12:30

Presentation about SSBP 2026, Edinburgh, UK

12:30 – 13:45

LUNCH & POSTER VIEWING

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13:45-14:45	SSBP AGM and Award Ceremony
	Session 11. Chair: Anna Jansen
14:45 – 15:30	Free Communications - 3 x 15 minutes
	43. Claudia Vingerhoets - Anxiolytic effects of riluzole in 22q11.2 deletion syndrome
	44. Danielle Baribeau - An N-of-1 trial of Fluoxetine in KCNC1 related disorder
	45. Lucas Gabriel Gutiérrez Lafrentz - TANDem-2: Closing the Gap to Interventions for TAND – study protocol
15:30 – 16:00	AFTERNOON REFRESHMENTS
	Session 12. Chair: Agnies van Eeghen
16:00 – 16:45	KEYNOTE: 46. Professor Marianne van den Bree - Improving care for people with rare genetic variants associated with neurodevelopmental conditions: contributions large longitudinal research cohorts can make
16:45 – 17:00	Closing Remarks
17:00	Closure of research symposium

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Abstracts for Educational Day

4th September *(in order of presentation)*

1. KEYNOTE: TSC - Our Journey with a Rare Disease

Presenting Author: Jan-Paul Wagenaar

Wagenaar J.-P.¹

¹ *Stichting Tubereuze Sclerose Nederland, the Netherlands*

Tuberous sclerosis complex (TSC) is a rare genetic disorder that results in many physical health problems involving growths throughout the body and hard-to-treat epilepsy. In addition to these physical challenges, TSC is associated with a wide range of other challenges, behaviour being one of them.

The Dutch TSC-patient advocacy group 'Stichting Tubereuze Sclerose Nederland' (STSN) was founded in 1981. The goal of the STSN was to improve diagnosis and treatment of TSC. Incorporating patient perspectives, using a bottom-up approach is critical for the STSN. From early on it was clear that dealing with complex and difficult behaviour was one of the biggest challenges for people with TSC and their parents and caretakers. This presentation will give an overview of the activities the STSN initiated, took part in and encouraged over time to increase the perspective of parents and caretakers to deal with the 24/7 task to improve the quality of life of people with TSC and complex behaviour. The first activities included starting a TSC & behaviour work group, raising awareness amongst behavioural experts and (co-)producing specific communications on TSC and behaviour. Next was to connect to experts working on behavioural aspects of TSC. Results included detailed descriptions of categorized TSC-cases and practical guidelines for parents and caretakers. At the same time the STSN took part and informed scientific research initiatives. To maximize the relevance of outcomes, where applicable, patients or caretakers were involved.

The presentation will highlight perceptions, priorities and ideas of people with TSC and their parents and caretakers, and their impact on both the design, research and implementation of services. In the last 30 years encouraging progress has been achieved regarding TSC and behavioural problems. Individual cases require tailor made approaches, and there are no general solutions for the many different practical challenges of TSC and complex behaviour. It is important to keep creating awareness and to offer parents and caretakers an overview of ever-changing, realistic pathways towards care and support.

Keywords: Tuberous Sclerosis Complex (TSC), Behavioural problems, Patient perspective, Practical guidelines, Advocacy

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2. KEYNOTE: Transition from Youth to Adult Care, Most Recent Insights and Future Challenges

Presenting Author: Therese van Amelsvoort

van Amelsvoort T.¹

¹ School Mental Health & Neuroscience, Maastricht University, the Netherlands

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The transition from adolescence to adulthood is a developmental process characterized by changes in legal status and social roles, which unfortunately often coincides with transfer of care from Child and Adolescent Mental Health Services (CAMHS) to Adult Mental Health Services (AMHS) in case of mental health problems. Adolescence constitutes a challenging time with profound physiological, psychological, and social-emotional changes. Adolescents and Young Adults (AYAs) are expected to take increased responsibility for their own lives and behaviour. They try to find their meaningful and contributive role in society, become financially independent and make their own decisions. AYAs negotiate relationships with family, peers and networks in new ways. At the same time, adolescence is a high-risk period for the emergence of mental disorders and alcohol / substance abuse. Brain development is ongoing, and maturation won't be complete before age 25. Taken together, service provision for AYAs with mental health problems continuity of care, instead of the traditional disruption is crucial. In this presentation the gap between CAMHS and AMHS and the vulnerability for mental ill-health in AYA will be highlighted. Psychiatrists should be aware of the different aspects of the transition from adolescence into adulthood. In addition, how to organize care i.e. how to prepare for transfer or how to provide continuity of care around age 18, how to meet the needs of young people, and transdiagnostic psychiatry will be addressed. Recent guidelines for transition of care will be discussed. Special attention will be given to the impact of the transition of care for AYAs with intellectual disabilities and / or genetic syndromes, who are at increased risk for mental health problems.

Keywords: Transition, youth, adult, mental health, genetic syndromes, intellectual disability

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3. KEYNOTE: Family-Oriented Care for Genetic Syndromes

Presenting Author: Janneke Zinkstok

Zinkstok J.¹

¹ Radboud University Medical Center Nijmegen Department of Psychiatry, and Karakter Child and Adolescent Mental Health Care Nijmegen, the Netherlands

Families caring for a child with a genetic syndrome often face significant challenges that affect their physical health, mental well-being, social functioning, and financial stability. Parents in particular must navigate the complexities of their child's care while coping with emotional experiences such as grief and loss related to their child's condition. Traditionally, treatment and support strategies have focused primarily on the individual with the genetic syndrome. However, growing evidence highlights the importance of supporting parental resilience as a pathway to improved outcomes for both children and families. This presentation will: 1) Examine the burden of care experienced by parents of children with genetic syndromes; and 2) Propose strategies to address this burden across syndromes. First, findings from a study on perceived caregiver burden among parents of children with Dravet Syndrome will be presented. Next, potential interventions will be explored, in particular design and preliminary findings of a pilot study on matched peer support for parents of children with neurodevelopmental disorders. The session will conclude with a call for systemic change, emphasizing the value of integrating parent-experts-by-experience into care frameworks. Given the substantial challenges faced by these families and the existing inequities in accessing support, there is a pressing need to better support parents of children, adolescents, and adults with genetic syndromes. This presentation aims to spark a conversation about how meaningful change can be initiated.

Keywords: Genetic syndromes, neurodevelopmental disorders, family-oriented care, peer support, participatory research

4. Mental Health Support Priorities for Families Caring for Children with Rare Genetic Conditions

Presenting Author: Jeanne Wolstencroft

Wolstencroft J.¹, Housby H.¹, Bhudia S.¹, Lee I.¹, Vainieri I.², Bennett S.³, Bednarczuk N.¹, Wynn S.⁴, Oliver B.R.⁵, IMAGINE-ID Consortium

¹ UCL GOS Institute of Child Health, UK

² Royal Holloway, UK

³ Kings College London, UK

⁴ UNIQUE, UK

⁵ UCL Institute of Education, UK

Background: The routine integration of next-generation sequencing technologies in the NHS has led to a rise in number of children diagnosed with a rare genetic condition (RGC) in early childhood (<6years). The risk of mental health conditions in this group is high, however anecdotal accounts suggest little support is provided. The present study aimed to (1) define the challenges and facilitators in accessing mental health support for families caring for RGC children and (2) explore family and healthcare professional priorities for mental health support.

Methods: A series of focus groups was conducted with parents of RGC children and neurodisability medical professionals. De-identified transcripts of interviews were analysed using Framework Analysis. Eleven parents of RGC children and four professionals participated in the focus groups.

Results: The framework analysis identified challenges related to having an RGC, including an absence of information in 'the big black hole' of the post-diagnostic void, 'falling between the cracks' and being 'stuck in a loop of referrals'. It also identified barriers that were specific to accessing mental health support if you have an RGC, including difficulties in understanding how to navigate services and diagnostic overshadowing. The RGC diagnosis often acted as an exclusion criteria for accessing mental health services. Facilitators in accessing mental health support included the parents' personal qualities such as resilience, happenstance, finding key advocates and getting other diagnoses that were more widely recognised. Parent and practitioner priorities for support were aligned. They included support for families in the 'post-diagnostic void', training and education for healthcare professionals and care co-ordination.

Conclusion: RGC children diagnosed in early childhood and their caregivers face unique challenges in accessing mental health support. Innovative approaches are needed to support parents caring for a child diagnosed with RGC in early infancy and to provide better training for professionals on RGC management.

Keywords: Rare disorder, mental health, genetic, neurodevelopment, service improvement

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5. Family Emotional Climate is Associated with Neuropsychiatric Outcomes in Young People with Neurodevelopmental Risk Genetic Conditions

Presenting Author: Josephine Haddon

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Background: A range of rare mutations involving micro-deletion or -duplication of genetic material (copy number variants (CNVs)) have been associated with high neurodevelopmental and psychiatric risk (ND-CNVs). Emotional climate within a family can be crucial in either mitigating or amplifying risk of psychiatric conditions, making it an important focus in prevention and intervention strategies. Here we examine the association between family emotional environment and mental health outcomes in a large population of children and young people with a range of ND-CNVs.

Methods: Family Cohesion and Conflict and parental caregiver-child Warmth and Hostility were assessed in 675 children with ND-CNVs and 276 sibling controls, using the Family Environment Scale and Behavioural Affect Rating Scale. Broader psychopathology, autism and intelligence quotient were assessed using the child and adolescent psychiatric assessment, social communication questionnaire, and Wechsler abbreviated scale of intelligence, respectively.

Results: Different family emotional climates were observed in ND-CNV families compared to reported norms: characterised by higher Family Conflict and Family Cohesion, decreased caregiver-child Warmth, and reduced Hostility between parents and their children with ND-CNVs. Family Conflict and caregiver-child Hostility were associated with an *increase* in Externalising and Internalising symptoms, whereas Family Cohesion and caregiver-child Warmth were associated with a *reduction* in Externalising symptoms in children with ND-CNVs. No associations were found between any family emotional climate measure and IQ. Children with ND-CNVs demonstrated greater sensitivity to family emotional climate, with a stronger impact observed on their mental health outcomes compared to controls. This was true more broadly across multiple psychiatric domains.

Conclusion: These findings underscore the importance of targeting family emotional climate in managing and preventing mental health outcomes in children with ND-CNVs. Families may benefit from support targeted at encouraging a positive emotional environment. For example, multidimensional family therapy and family-based physical activity interventions.

Keywords: Clinical genetics, Human behaviour, Family Emotional Environment, Intervention

6. Psychopharmacology in Children with Genetic Disorders of Epigenetic and Chromatin Regulation

Presenting Author: Danielle Baribeau

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Background: Hundreds of rare genetic variants associated with autism or intellectual disability have been identified, and many impact genes known to have a primary epigenetic/chromatin regulatory function. The objective of this study was to examine and compare behavioural profiles and longitudinal psychotropic treatment patterns in children with epigenetic/chromatin variants, other rare variants impacting neurodevelopment, or no known genetic condition.

Methods: Using electronic medical records from a paediatric psychopharmacology program for children with autism or intellectual disability, we compared clinical characteristics, longitudinal psychotropic medication profiles and side effects between those with and without a rare genetic variant, and by variant subtype [epigenetic/chromatin regulation or other variant].

Results: A total of 331 children attended 2724 unique medical visits between 2019 and 2022, with a mean of 8 follow-up visits over 3.4 years. Nine children (3%) had variants in epigenetic/chromatin regulatory genes (EC), twenty-three children (7%) had other rare genetic variants (OTH), and the rest had no reported variant (NR, n = 299, 90%). Those with a rare genetic variant (EC or OTH) were more likely to have an intellectual disability and had a greater number of co-occurring physical health conditions ($p < 0.01$). Overall, 66% of psychotropic medications were continued for ≥ 3 visits, while 26% were discontinued. Rates of psychotropic polypharmacy, medication patterns, behavioural challenges, and co-occurring developmental diagnoses were similar between genetic groups. Analyses uncorrected for multiple comparisons suggested those with genetic variants were more likely to experience drowsiness/sedation as a side effect (EC 33%, OTH 35%, NR 16%, $p < 0.05$); weight gain as a side effect was also higher in the epigenetic/chromatin group (EC 50% vs OTH 11%).

Conclusion: Genetic classification of neurodevelopmental disorders (NDDs) may help anticipate treatment tolerability; additional prescribing considerations may be needed for those with rare variants. Current psychotropic prescribing practices do not differ across rare genetic NDD subgroups.

Keywords: Autism, psychopharmacology, methylation disorder

7. KEYNOTE: Care for Genetic Obesity – Experiences from the Dutch Expert Center for Genetic Obesity

Presenting Author: Mieke M. van Haelst

Van Haelst M.M.^{1,2,3}

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Background: Syndromic obesity is the umbrella term for disorders associated with obesity and intellectual disability (ID), dysmorphic features, and/or developmental abnormalities of specific organs or organ systems. At our expert centre for genetic obesity in Amsterdam UMC and Erasmus MC we perform extensive genetic diagnostics in patients with syndromic obesity. I will present a case series of several of our most remarkable cases, either because of the interesting diagnostic journeys or the effect of the diagnosis on treatment.

Methods: After intake at our clinic, extensive genetic diagnostics are performed, ranging from chromosomal microarray to (trio) whole exome sequencing, and methylation tests. In cases where variants of uncertain significance (VUS) are found, we assess whether pathogenicity can be confirmed by using the EpiSign DNA methylation test. After the molecular diagnosis we evaluate if there are treatment options or clinical trials available for the specific disorder.

Results: I will present how patients were diagnosed, and the effect of the diagnosis. EpiSign tests helped us diagnose patients with VUS in obesity genes. For specific conditions, hormonal treatments became available after diagnosis, such as growth hormone therapy for Temple syndrome. We were able to invite patients with 16p11.2 deletion syndrome, Bardet-Biedl syndrome, Chung-Jansen syndrome, and Schaaf-Yang syndrome to participate in clinical trials with anti-obesity medication.

Conclusion: Syndromic obesity represents a diverse group of conditions in which obesity is accompanied by a variety of syndromic features. Understanding the underlying genetic and molecular mechanisms is crucial for diagnosis, support, and treatment of the affected individuals. At our Emma Center for Personalized Medicine we aim to further accelerate diagnostics and therapy development for these rare conditions.

Keywords: Genetic obesity, Intellectual disability, personalized treatment

8. Longitudinal Development of Prodromal Psychosis in Young People at High Genomic Risk of Schizophrenia

Presenting Author: Jessica Hall

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Background: Several copy number variants (CNVs) confer high risk for psychosis (PR-CNVs), providing the opportunity to investigate emergence of psychotic phenomena and predictors across development. Understanding how prodrome manifests in this genetically at-risk population may inform intervention strategies and clinical decision-making for young people with and without PR-CNVs.

Methods: This longitudinal study of young people with existing diagnoses of PR-CNVs, examined the association between prodromal psychosis and psychiatric symptom trajectories. Data were collected from 320 individuals with 10 different PR-CNVs and 125 sibling controls (age 7-25) across 1-5 timepoints. Prodromal psychosis status was assessed via the Structured Interview for Prodromal Syndromes (SIPS). Symptom counts for ADHD, anxiety, and sleep disturbances were measured using the Child and Adolescent Psychiatric Assessment, autism symptoms via the Social Communication Questionnaire, and cognitive ability with the Wechsler Abbreviated Scale of Intelligence. Linear mixed-effects models were applied to contrast psychiatric and cognitive trajectories based on prodromal status.

Results: Individuals with PR-CNVs were more likely to meet criteria for prodrome (33.1%) compared to controls (6.4%) (OR = 8.06, $p < 0.001$). Prior psychotic experiences (PEs) did not predict prodrome (OR 1.63, $p = 0.148$). Individuals who developed prodrome had trajectories of high symptoms across development in ADHD ($\beta = 0.39$, $p < 0.001$), anxiety ($\beta = 0.34$, $p < 0.001$), indicative autism ($\beta = 0.27$, $p = 0.004$), and sleep disturbances ($\beta = 0.40$, $p < 0.001$). Prodromal status was not associated with the trajectory of intellectual functioning.

Conclusion: Prodromal psychosis prevalence is high in PR-CNV carriers. While prior PEs did not predict prodrome, elevated symptoms of ADHD, anxiety, autism, and sleep disturbances may signal increased early risk. This highlights limited specificity of PEs alone and suggests the need for transdiagnostic monitoring. Early intervention for psychosis mitigates severity; given the practical constraints of monitoring all children with rare variants, these findings help identify subgroups at heightened risk who may benefit from closer surveillance—potentially extending beyond PR-CNVs.

Keywords: Prodromal psychosis, Copy Number Variants, Psychiatric trajectories, Psychosis risk

9. The Added Value of Using Infographics on the Educational and Psychosocial Needs of Children and Adolescents with 22q11 DS in School: The Leuven Experience

Presenting Author: Ann Swillen

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Background: 22q11.2 deletion syndrome (22q11.2DS) is a complex and widely variable genetic syndrome involving multisystem physical health problems, significant cognitive and psychosocial challenges, all of which may have an impact upon learning and academic achievement. Children with 22q11.2DS require increased and specific educational/psychosocial support to fully participate in their learning/school environments. Since many years, parents and school teams point to the great need for better understanding of the educational and psychosocial needs of children with 22q11.2DS.

Method: To provide an answer to this urgent need, we developed a psychoeducational tool namely infographics on the educational and psychosocial needs of children and adolescents with 22q11 DS for the preschool, primary and secondary school period. Both information from parents, school teams and 22q11 DS experts were taken into account. Our aim is a) to increase knowledge in educators on the educational and psychosocial needs of children with 22q11 DS in the school context and 2) to facilitate communication between parents and the school team.

Results: Since the launching of the infographics (on papier and digital) in Spring 2025, many families (> 100) with a child/adolescent with 22q11 DS and schools are using the infographics. All parents and school teams report more understanding of the educational and psychosocial needs of a child with 22q11 DS in the school context. Parents report that the communication with the teacher/school team has become easier, and their relationships have become more positive. Teachers report more clear communication and improvement of full collaboration of all education personnel involved.

Conclusion: The use of infographics on the educational and psychosocial needs of children with 22q11 DS in school increases the knowledge in school teams, facilitates and supports communication between parents and teachers, and contributes to integrated and tailored educational/psychosocial care for children & adolescents with 22q11 DS at school.

Keywords: Educational and psychosocial needs, 22q11 DS, psychoeducation, infographics, integrated and tailored educational and psychosocial care

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10. TRICXY-MINDS: Clinical Insight into Sex Trisomies for Enhanced Psychiatric Care in Individuals with X and Y Chromosomal Aneuploidies in Norway

Presenting Author: Ida Elken Sønderby

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Background: 1 in 400 is born with an atypical number of sex chromosomes (sex chromosome aneuploidies (SCAs)). Only ~25 % are genetically detected; mostly due to somatic symptoms. Many experience behavioural challenges including social interactions, reflected in odds ratio for several mental disorders of >2. This indicates a substantial subgroup in the psychiatric services (1-2 in 200 patients) that may have specific characteristics with potential for precision medicine. However, lack of data and huge heterogeneity has hindered the development of tailored guidelines for care and specific interventions.

Methods: TRICXY_MINDS will map disease and health trajectories of >500 Norwegian SCA carriers representing an estimated 3-4% of Norway's SCA population. Using well-established Norwegian population and clinical samples including the longitudinal Norwegian mother, father and child cohort, MoBa (n=260,000), we will establish detailed young and adult health profiles of SCA carriers. We will adapt a social management training (SMT) for Klinefelter developed in the Netherlands and designed to target improvement of cognitive functions to enhance mental health. In our SCA clinical sample, we mapped autistic symptomatology (Social Responsiveness Scale (SRS)), behavioural and emotional profiles (Developmental Behaviour Checklist, Symptom Checklist-90-R). We will compare to the profile of individuals with autism or other rare genetic disease groups with high risk of mental disorders.

Results: Data indicated that adult individuals with clinically detected Klinefelter, 47,XYY and 47,XXX have higher levels of autistic symptoms in comparison to individuals with Turner (45,XO). Likewise, data showed that individuals with SCAs from the MoBa pregnancy study, followed from birth and until late teens, have approximately twice as many mental (ICD-10 F-) diagnoses in comparison to individuals without SCAs.

Conclusion: Moving forward, the Norwegian TRICXY_MINDS project will provide a broad population-wide mapping of individuals with SCAs while contributing to new knowledge on treatment through its social management training.

Keywords: Klinefelter, population study, social management training

11. KEYNOTE: Clinical Practice Guidelines for Rare Genetic Conditions Associated with Intellectual Disability

Presenting Author: Mirthe J. Klein Haneveld

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Rare genetic conditions associated with intellectual disabilities can significantly impact physical and psychosocial functioning, often requiring lifelong and multidisciplinary care. Due to the complexity and rarity of these conditions, providing appropriate care for this population can be challenging for healthcare professionals.

Clinical practice guidelines offer evidence-based recommendations for the diagnosis and management of conditions, aimed at supporting healthcare professionals in their daily practice. However, developing such guidelines for rare conditions presents unique difficulties, such as lack of scientific evidence. This presentation will outline the guideline development process and international standards for guideline methodology, including GRADE (Grading of Recommendations, Assessment, Development and Evaluation) and AGREE (Appraisal of Guidelines for Research & Evaluation).

Each step of the development process will be discussed in the specific context of rare genetic conditions and/or individuals with intellectual disabilities. Topics will include dealing with limited evidence in rare disease settings, translating evidence into recommendations while integrating the values of individuals and families, and fostering collaboration between clinical experts and patient advocates. Practical examples will be drawn from ongoing work within the European Reference Network ITHACA and related research projects. As such, this presentation aims to support those who use clinical practice guidelines in their daily practice or contribute to their development as researchers or clinical experts.

Keywords: Clinical practice guidelines, evidence-based medicine, methodology, genetic syndromes, rare disease, intellectual disability

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12. Exploring the Role of Parental Cognitive Skills on 36-month Outcomes in Children with Prenatally Diagnosed XXY, XYY, and Trisomy X

Presenting Author: Nicole Tartaglia

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Introduction: Sex chromosome trisomy (SCT) — including XXY, XYY, and Trisomy X — is associated with increased risk for cognitive and learning challenges. With rising prenatal detection through cell-free DNA testing, there is growing interest in understanding predictors of developmental outcomes. While correlations between parent and child cognitive skills are established in the general population, this relationship has not been explored in SCT. This study examined whether parental cognitive abilities are associated with developmental outcomes at 36 months in children enrolled in the *eXtraordinary Babies Study*, a prospective study of children with prenatal SCT diagnoses.

Methods: Infants with SCT were enrolled before 12 months and underwent annual evaluations. At 36 months, assessments included the Bayley-3 Scales (cognitive, language, motor domains) and the NIH Toolbox Receptive Vocabulary Test. Parents completed the NIH Toolbox Cognition Battery, including Crystallized (vocabulary, reading) and Fluid (executive function, working memory, processing speed) composites. Pearson correlations were used to assess associations ($p < 0.05$).

Results: Participants who completed a 36-month visit and at least one parent NIH Toolbox assessment were included; 110 children (72 XXY, 10 XYY, 28 XXX) and 153 parents (99 mothers, 54 fathers). No significant differences in child or parent scores were found across karyotypes, so groups were pooled. Results showed small to moderate correlations ($r = 0.22-0.46$) between parent NIH Toolbox crystallized composite scores and child Bayley-3 and NIH Toolbox receptive vocabulary results. Parental IQ more strongly predicted Bayley-3 language domains, followed by cognitive and motor domains. Correlations of paternal scores were stronger than maternal scores for all domains. There were no significant correlations between parental Fluid Composite scores and child 36-month scores.

Conclusion: Parental verbal abilities (vocabulary and reading) are positively associated with 36-month developmental outcomes in children with SCT. Paternal cognition showed stronger associations compared to maternal scores, though selection bias of the paternal cohort may contribute. Future analyses with larger cohorts and older age groups will further explore these relationships and other predictive factors, including family history of learning or attention disorders.

Keywords: XXY, Klinefelter, XYY, Trisomy X, Sex Chromosome

13. Advancing Detection of Social Anxiety in Fragile X Syndrome: A Multi-Method Exploration of Social Behaviour, Heart Activity, and Heart Rate-Defined Sustained Attention

Presenting Author: Kayla Smith

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Background: Social anxiety is highly prevalent in people with fragile X syndrome (FXS). Identification and diagnosis in FXS is challenging due to a complex social profile of socially anxious and motivated behaviours and may be further complicated by physiological hyperarousal and reduced social attention. This study aims to characterise behavioural, physiological, and cognitive indicators of social anxiety in people with FXS.

Methods: Participants included 21 people with FXS ($Mdn_{age} = 23.13$ years). Social anxiety and social motivation behaviours were rated during naturalistic social presses (voluntary social interaction, required social interaction, performance) using the Social Anxiety and Social Motivation Rating Scale. Physiological indices included respiratory sinus arrhythmia (RSA), interbeat intervals (IBI), and RSA suppression (i.e., difference in RSA from press to baseline condition) during each press. Social attention was assessed using heart rate-defined sustained attention (HRDSA). Parent-reported social anxiety was assessed using the Anxiety Disorders Interview Schedule – Autism Addendum.

Results: Spearman correlations revealed social anxiety behavioural scores during the voluntary social interaction press ($r_s(19) = .441, p = .046$) and RSA during the voluntary ($r_s(11) = .763, p = .002$) and required social interaction presses ($r_s(11) = .641, p = .018$) were significantly associated with parent-reported social anxiety. No significant associations were found for social motivation behavioural scores, IBI, RSA suppression, or HRDSA indices (p s $\geq .101$).

Conclusion: Greater observed social anxiety and higher RSA in low-demand social contexts were linked to greater parent-reported social anxiety. Neither IBI, RSA suppression, nor HRDSA were associated with social anxiety, potentially attributable to general phenotypic physiological hyperarousal and other factors of social attention. Identifying and characterising indicators of social anxiety and motivation will inform the social profile observed in FXS and lead to hypotheses around the mechanistic underpinnings of the prevalence and severity of social anxiety, which is essential to early detection and intervention.

Keywords: Fragile X syndrome, social anxiety, social motivation, behaviour, heart activity, heart rate-defined sustained attention

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Abstracts for Research Symposium

5th – 6th September *(in order of presentation)*

14. KEYNOTE - THE TOM OPPÉ DISTINGUISHED LECTURE:

What are the Gaps in Research for the Communities of People with Down Syndrome, Fragile X Syndrome and Williams Syndrome?

Presenting Author: Emily Farran

Farran E.¹

¹ School of Psychology, University of Surrey, UK

There are approximately 1.5 million people in the UK with a learning disability. These individuals and their communities should have a role in shaping the research that impacts them. To meet that need, we completed the “Shape Research, Change Lives” project. We compared the UK research landscape to the research priorities for individuals with Down syndrome (DS), Fragile X syndrome (FXS), and Williams syndrome (WS). Key findings were that £26 million was spent on research on DS, FXS and/or WS between 2013 and 2022 in the UK, representing <1% of UK funders’ portfolios. Most research was on basic science (brain, body and cognition), with the least research funding being spent on lifespan issues, societal issues, and research infrastructure. We consulted with the DS, FXS and WS communities on their research priorities via online focus groups and surveys. We found that DS, FXS, and WS communities were dissatisfied with the current research portfolio. Survey responses and thematic analysis of focus groups indicated that: they weighted research that will affect their everyday lives equally important to basic science; that research should be accessible to all; and that research should be informed by people with lived experience. Priority-setting exercises like the current study allow funders and researchers insight into areas of research that should be targeted because they are prioritised by the community in question. As a team, we are raising awareness of the mismatch between the current research landscape and the research priorities of the communities, and are starting to address this in our own studies. I will end the presentation by briefly introducing our ongoing work.

Keywords: Learning disability; Down Syndrome; Fragile X Syndrome; Williams Syndrome; Priority Setting

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15. THE PAT HOWLIN PRIZE: Cognitive Behavioural Therapy in Adolescents with Fragile X Syndrome: A Feasibility Randomized Controlled Trial

Presenting Author: Alice Federica Maria Montanaro

Montanaro F.A.M.^{1,2}, Caciolo C.², Spano G.³, Bosco A.¹, Vicari S.², Alfieri P.²

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Background: Adolescents with Fragile X Syndrome (FXS) often experience significant psychosocial challenges; however, research on the feasibility and effectiveness of behavioural interventions for this population remains limited. Additionally, many existing studies lack methodological rigour, and no randomized controlled trials (RCTs) have been conducted to date. Using a pilot randomized delayed intervention-controlled trial, this study aimed to evaluate the clinical efficacy and feasibility of a group cognitive-behavioural therapy (CBT), named Cooperative Group Therapy (CGT), in adolescents with FXS. For transparency, the study has already been registered on clinicaltrials.gov (NCT06677866).

Methods: Ten adolescents with FXS and moderate intellectual disability (ID) were recruited and assigned to one of two groups: (1) FXS-CGT, receiving immediate treatment, and (2) FXS-WL, a waitlist control group receiving the intervention after a six-month delay. Standardized assessments and blinded neuropsychiatric evaluations were conducted at baseline (T0) and post-intervention (T1). The FXS-CGT group has completed the intervention, while the FXS-WL group is currently undergoing the final sessions. This study presents preliminary findings.

Results: Preliminary data indicate that the FXS-CGT group exhibited reduced clinical illness severity, decreased anxiety, and improved social-adaptive skills compared to the FXS-WL group. Additionally, reductions in parenting distress and improvements in family quality of life were observed following the intervention in the treated group.

Conclusion: This study represents the first RCT investigating the feasibility of CBT for adolescents with FXS. Findings suggest that group CBT may be a promising intervention for addressing the cognitive-behavioural phenotype of FXS, particularly during adolescence, when environmental demands increase. Further research with larger samples is warranted to validate these preliminary results.

Keywords: Fragile X syndrome; CBT therapy; intellectual disability; social skills; adaptive behaviour; neurodevelopmental disorders

16. Molecular, Neurocognitive and Psychosis Risk Profiles in Youth and Young Adults with 22q11.2 Deletion Syndrome: Longitudinal Findings from a Multimodal Study

Presenting Author: Flora Tassone

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Background: 22q11.2 Deletion Syndrome (22q) is a multisystemic disorder of known genetic aetiology with high penetrance and variable expressivity, leading to a wide spectrum of clinical manifestations, including complex neurocognitive and psychiatric profiles. This study presents updated findings from a longitudinal cohort (ages 16–26) examining cognitive-affective predictors of psychosis-proneness and adaptive functioning and explores the role of metabolic alterations as potential modifiers.

Methods: Data was collected from 26 participants (n = 26; 16 with 22q, 10 TD controls) using a standardized battery (NIH Toolbox: Cognition and Emotion), cognitive assessment (WASI-2), structured psychiatric interviews (SIPS, KSADS/SCID-5), and molecular biomarker analyses.

Results: Full-Scale IQ scores for participants with 22q ranged from 60–127 (M = 87.0, SD = 23.69). A consistent pattern showed lower Perceptual Reasoning relative to Verbal Comprehension, highlighting challenges in nonverbal reasoning and visuospatial processing. Executive functioning was notably affected, particularly in tasks requiring cognitive flexibility and inhibitory control (Flanker: M = 79.1; Dimensional Change Card Sort: M = 82.4). Deficits in processing speed and working memory further reinforced known vulnerabilities in attentional and executive systems. Importantly, 18% met criteria for Attenuated Positive Symptom Syndrome at both timepoints, with most showing stable or slightly improving symptoms, though a subset worsened over time. Executive dysfunction and emotional dysregulation under negative affective load were considered strong predictors of psychosis-proneness. Preliminary metabolic/proteomic profiling (e.g., reduced taurine and arachidonic acid, increased proline levels) revealed untargeted metabolic markers and alterations that may distinguish deletion carriers from controls and serve as early predictors of psychosis vulnerability before symptom onset.

Conclusion: These findings underscore the importance of early cognitive and emotional markers in identifying youth with 22q at elevated risk for psychosis. Future directions include validating biomarkers and optimizing targeted early interventions to improve long-term neuropsychiatric outcomes.

Keywords: 22q11.2 DS, psychosis risk, executive functioning, NIH Toolbox, biomarkers, metabolomic, longitudinal study

17. Gene Therapy in Fragile X Syndrome: A Caregiver Perspective

Presenting Author: Sarah Eley

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¹ The Patrick Wild Centre, University of Edinburgh, U.K.

Background: There have been increasing numbers of clinical trials of medications for Fragile X syndrome (FXS) in recent years. Genetic therapies represent a different approach, which aim to address the genetic mechanisms by which FXS arises. While not tested in humans for FXS, they are a growing focus in neurodevelopmental research. It is important that families affected by FXS get the chance to give their views about future genetic therapies, given this can be a controversial project.

Methods: We developed a questionnaire to capture caregiver views around gene therapy in FXS. The questionnaire was developed alongside a group of caregivers of a child with FXS. The questionnaire contained questions around current knowledge, what families think of gene therapy and their views on trials taking place. Responses were analysed by thematic analysis.

Results: The questionnaire was completed by 195 individuals who are parents of, or who care for, someone with FXS. Respondents were primarily from the UK (60.5%) and the Americas (22.1%). The majority of dependants were male (86%). Responses showed a strong interest from the Fragile X community in gene therapy trials taking place (94% in favour). 67% of respondents would consider gene therapy as a treatment option for the person they care for, with age of dependant significantly affecting this response (>16 less likely). Themes emerged around quality of life, outcomes and feelings. Hope for positive change was balanced against caution about unintended consequences, the newness of the treatment and tolerability.

Conclusion: Overall, caregivers felt hopeful, excited and interested in the prospect of gene therapy potentially providing a new treatment option, there was some trepidation about the potential effects. Taking caregiver views into account will help inform decisions around the development and testing of any future genetic interventions.

Keywords: Gene therapy, Fragile X Syndrome, qualitative, questionnaire, views, treatment

18. KEYNOTE: Statistical Challenges of Trials in Rare Genetic Disorders

Presenting Author: Peter M. van de Ven

van de Ven P.M.¹

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Performing intervention studies in rare genetic disorders is challenging, both because of the limited number of available study participants and heterogeneity in their phenotypes. Methodological and statistical solutions proposed for trials in small populations in literature and guidelines may tackle these challenges to some extent. Depending on the clinical indication, therapy and endpoint, increases in power can generally be achieved by adjustments for prognostic baseline covariates, the use of repeated measurements of the outcome variable and through the use of within-subject designs. Despite this, performing adequately powered studies to show the benefit of therapies in rare genetic disorders remains challenging or may not even be possible. Individualization of therapies and endpoints poses additional challenges for obtaining evidence on effectiveness of therapies in rare genetic disorders. In my talk, I will discuss the most important methodological and statistical challenges for both generic and individualized therapies and present some potential solutions with their strengths and limitations.

Keywords: Trials, rare diseases, Bayesian statistics, within-subject designs, intervention research, single-case experimental designs

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19. Development and Validation of the Klinefelter-Associated Neurodevelopmental Difficulties (KAND) Checklist: A Three-Phase Mixed-Methods Study

Presenting Author: Kaat Theelen

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Background: Klinefelter syndrome (KS) (47,XXY) is a genetic condition linked to infertility, hormonal imbalances, and various neurodevelopmental and psychosocial challenges, including language impairments, executive dysfunction, and difficulties in social functioning. Although these challenges can significantly affect daily life, no uniform terminology or standardized tool currently exists to systematically identify and assess them. Building upon research in tuberous sclerosis complex (TSC), this study explored the neurodevelopmental difficulties associated with KS and developed, validated, and translated the Klinefelter-Associated Neurodevelopmental Difficulties (KAND) Checklist.

Methods: A three-phase mixed-methods approach was used. In Phase 1, a literature review and semi-structured interviews with nine adults with KS and eleven parents identified relevant difficulties and informed adaptation of the TAND Checklist, resulting in the preliminary KAND Checklist. In Phase 2, qualitative and quantitative feedback from thirteen healthcare professionals, twenty-four parents, and a focus group with parents guided iterative revisions, leading to a pre-final version. In Phase 3, the checklist was validated with eighteen individuals with KS and twenty-nine parents using validated behavioural measures, psychometric testing, and feedback. The final KAND Checklist was translated through a forward-backward process.

Results: The final checklist demonstrated good internal consistency and external validity. Content was adapted to address KS-specific challenges, with expanded sections on language and communication, psychosocial functioning, communication about the diagnosis, and family impact. Enhancements in face, content, and response process validity were observed across all phases, improving comprehensiveness, usability, and clarity.

Conclusion: The KAND Checklist is a reliable tool for identifying neurodevelopmental difficulties in individuals with KS. It raises awareness, facilitates structured clinical conversations, and encourages individualized care. This study highlights the value of participatory research in developing health tools, promoting inclusive healthcare, and fostering multidisciplinary collaboration between patients, their families, and professionals. Further dissemination, translation, and validation in larger cohorts are needed to ensure broad adoption in clinical and research settings.

Keywords: Klinefelter syndrome, Wellbeing, Neuropsychological, Psychosocial, Participatory research, Self-report

20. PROM4RARE: The Final Core Patient Reported Outcome Set for Individuals with Genetic Intellectual Disability

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Background: To improve care and research for individuals with genetic intellectual disability (GID), it is essential to measure relevant patient reported outcomes (PROs), which reflect patients' perspectives on their health. However, various and potentially irrelevant PROs are measured for individuals with GID. Therefore, the aim of this study is to identify most relevant PROs and develop a generic core PRO set for GID to be used in care and research.

Methods: PROs identified through a literature review, as well as focus groups and interviews with individuals with GID, caregivers, and experts, were integrated and operationalised into a pilot core PRO set with an expert group. This set was presented in a two-round Delphi survey with individuals with GID, caregivers, and experts. Consensus was set at 60% or more of all participant groups rating a PRO as important for inclusion in the final core PRO set, or as not important for exclusion. The Delphi surveys were followed by two consensus meetings with individuals with GID, caregivers, and experts to reach consensus on the undecided PROs.

Results: Twelve individuals with GID, 21 caregivers, and 28 experts (total n = 61) participated in the first Delphi round. Twenty-nine PROs were presented to the participants. In the first round, consensus was reached on one important PRO 'fatigue'. In the second Delphi round, consensus was reached on 12 important PROs, including sleep, depressive symptoms, and communication, among others. Consensus meetings resulted in agreement on seven additional important PROs (e.g., pain, anxiety), resulting in a final core set of 19 PROs.

Conclusion: This study identified 19 key PROs for GID, marking the final step in developing a generic core PRO set. These PROs should inform care, research, and policymaking. The next step involves selecting and validating suitable patient reported outcome measures (PROMs) to measure these PROs.

Keywords: Genetic intellectual disability, patient reported outcomes, patient reported outcome measures

21. COS4TAND: Towards a Core Outcome (Measure) Set for TSC-Associated Neuropsychiatric Disorders (TAND)

Presenting Author: Floortje Hosman

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Background: TSC-Associated Neuropsychiatric Disorders (TAND) include a diverse range of behavioural, psychiatric, intellectual, neuropsychological, psychosocial and academic manifestations that affect most individuals with TSC. The complexity and diversity of TAND symptoms requires outcome measures that can help diagnose, monitor, and evaluate treatments in clinical research and care. Currently, many different and potentially irrelevant outcomes are measured for TAND, with varying outcome measures and measurement properties.

Methods: We aim to harmonize TAND data in research and care by 1) reaching consensus on most important TSC outcomes to establish a Core Outcome Set (COS), and 2) selecting suitable outcome measures to establish a TAND Core Outcome Measures Set (COMS). The following steps will be taken: a) Gaining insight into currently used TAND measures by a1) surveying TSC clinics, and a2) performing a systematic review on measurement properties of TAND measures; b) Reaching consensus on relevant outcomes for individuals with TSC and establish a TSC COS including core Patient Reported Outcomes set by: b1) performing a scoping review, b2) doing focus groups and interviews with patients, caregivers and clinicians, b3) discussing outcomes with an expert group, and b4) performing a two-round Delphi survey and consensus meetings; c) Selecting outcome measures and establish a TAND COMS including core Patient Reported Outcome Measures (PROM) set by: c1) using the results of "step a" and the COSMIN checklist, and c2) selecting feasible measures with good measurement properties, and d) validating the core PROM set as part of the TAND COMS.

Conclusion: In this protocol, the steps required to establish a TAND COMS, including core PROM set, are presented. The TAND COMS eventually needs to be implemented in research and care in order to facilitate the interpretation, comparability and analysis of relevant TAND outcome data. The core PROM set will ensure the integration of the patient perspective.

Keywords: TSC, TAND, COS, PROM

22. Concept Formation as a Cognitive Outcome Measure in Rare Diseases

Presenting Author: Aaron Kaat

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Background: Concept formation—or the ability to identify relationships among objects within and between categories—is a pivotal cognitive skill that develops early in life and is foundational to engaging in more complex cognitive tasks. It develops rapidly among neurotypical preschoolers, but attainment of it may be protracted in children with genetic conditions associated with neurodevelopmental disorders (GCAND). This makes concept formation an attractive treatment target for clinical trials, as it may be more sensitive to change. Unfortunately, it is inconsistently measured by existing cognitive tests. We created a 50-item new test pilot version intended to assess concept formation for use in future clinical trials among those with GCAND.

Methods: We recruited 55 individuals with GCAND, 17 neurotypical controls, and 27 children at risk for a neurodevelopmental diagnosis through various existing research protocols. Concept Formation was administered, as well as protocol-specific measures that could provide convergent validity evidence (e.g., the Vineland-3, Weschler tests). Internal consistency was estimated using split-half reliability. A subsample of participants completed the test a second time to index test-retest reliability.

Results: The split half reliability was high ($r=0.99$ [0.98, 0.99]). A subsample of 19 took Concept Formation twice, among whom test-retest reliability was strong ($ICC=0.78$). No potential convergent validity measure exactly matched our conceptualization of Concept Formation and as such only moderate correlations were anticipated. This was largely supported (median $r=0.58$). Among the neurotypical comparison group, scores were also moderately correlated with chronological age ($r=0.73$).

Conclusion: Concept Formation is a test in-development for the purpose of assessing cognitive changes among those with GCAND. It is designed to assess foundational skills not normally assessed on existing measures, and to be sensitive to change. This study provides initial psychometric evidence supporting its use. We hope to continue to develop it, especially given the high need for such measures in upcoming clinical trials.

Keywords: Genetic Conditions Associated with Neurodevelopmental Disorders, Cognitive assessment, Clinical outcome assessment, Categorisation

23. Using Machine Learning to Explore Behavioural Phenotypes Across Single Gene Neurodevelopmental Conditions

Presenting Author: Lindsay Mizen

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Background: Hundreds of genes have now been linked to diagnoses of intellectual disability (ID) and behavioural phenotypes have been described for many genes associated with ID. However, there is significant overlap between conditions and it's not clear how successfully behaviour can be used to discriminate between them.

Methods: Using data from the Simons Searchlight project, an international repository for data from individuals affected by rare genetic neurodevelopmental conditions, we analysed data from the Child Behavior Checklist 6 to 18 (CBCL) questionnaire. 780 different probands were initially identified, which covered 94 different genes. A Principal component analysis (PCA) and k-means clustering were applied to the dataset. Machine Learning (ML) was then applied to a subset of genes with 20 entries or more (12 genes, 453 participants) to predict genetic status using the responses in the CBCL. Hyper-parameters were selected by Bayesian Optimisation.

Results: The gap statistic suggested that the CBCL data did not exhibit clustering on the principal components. The ML algorithm Extreme Gradient Boosting (XGBoost) performed the best at predicting gene, Accuracy > no information rate $p < 0.001$, achieving an accuracy 27.15%, macro precision 24.39%, recall 22.85%, and F1-score of 22.73%. The 3 most important features in the model were internalising characteristics t-score, withdrawn/depressed t-score and DSM5 anxiety / depression t-score.

Conclusion: We demonstrated that machine learning can be used to examine phenotypic clustering of different genetic conditions using each of the questions from the CBCL. The model outperformed chance levels of accuracy, but showed that there is significant overlap between the presentations of the genetic conditions. Going forward, we will seek to understand if there are particular questions on the CBCL which better discriminate between conditions and to explore whether other phenotypic information available in Simons Searchlight can be used to classify genotypes more accurately.

Keywords: SYNGAP1, Machine Learning, Simons Searchlight

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24. Social Functioning as a Predictor of Development in Adult Women with Triple X Syndrome

Presenting Author: Maarten Otter

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Background: Like in many other genetic syndromes, the behavioural phenotype of triple X syndrome (TriX) is described in children and adolescents, but not in adults.

Methods: In this cross-sectional study, data were collected from 34 women with TriX (mean age = 32.9; s.d. = 13.1) and 31 controls (mean age = 34.9; s.d. = 13.7). The Social Responsiveness Scale in Adults (SRS-A) was used to describe social functioning; the Wechsler Adult Intelligence Scale III-NL (WAIS III-NL) was used to estimate Full Scale IQ (FSIQ). The Cambridge Neuropsychological Test Automated Battery (CANTAB) was used to assess broader neurocognitive functioning; the MINI Neuropsychiatric interview and the Adult Behaviour Checklist (ABCL) were used to describe the prevalence of psychiatric disorders.

Results: Mild-to-moderate and severe deficits in social responsiveness were described in 37,5% of the TriX group and 3,3% in the control group. FSIQ appeared to be significantly lower in the TriX group compared to the control group. In addition, women with TriX had significantly more attention problems and lower psychomotor speed, particularly motor processing speed and decreased free recall in the verbal memory test. Women with TriX and impaired social functioning showed executive dysfunction in contrast with women with TriX and typical social functioning. In the TriX group, MINI results showed a higher prevalence of major depressive episodes (43.3%), psychotic disorders (29.4%), and suicidality (23.5%). Only 50% of the TriX group earned a normal score for the total syndrome score using the ABCL. Impaired social functioning appeared to represent a major risk factor in TriX as regards psychotic, affective disorders, trait anxiety, and low self-esteem.

Conclusion: Impaired social functioning appeared to be a risk factor for developing executive dysfunction and psychiatric disorders.

Keywords: Triple X syndrome, adults, social functioning, mental health, neurocognitive functioning, executive functioning

25. KEYNOTE: Bridging the Gap: Developing a Generic PRO Set for Individuals with (Genetic) Intellectual Disabilities

Presenting Author: Lotte Haverman

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Patient-reported outcomes (PROs) are increasingly recognized as essential for understanding the impact of disease and treatment from the patient perspective. PROs are assessed using patient-reported outcome measures (PROMs), which come in many forms: generic, disease-specific, symptom-specific, and population-specific. This diversity can lead to a proliferation of instruments that hampers comparability across studies and clinical settings. In the field of intellectual disability (ID), this issue is especially pronounced. As shown in the recent reviews by van Silfhout and Müller, the current landscape of PROMs in this population is highly fragmented, with wide variation in outcome definitions and instruments.

Over the past two decades, dr. Haverman has gained extensive experience implementing PROMs in clinical care and research. She contributed to the development of a generic PRO(M) set for the Dutch general population, covering domains such as anxiety, depression, fatigue, and social participation. Strikingly, these PROs showed strong overlap with those identified as relevant in populations with intellectual disabilities (ID), supporting the idea of generic outcome measurement and making it inclusive and equitable.

The development of a generic PRO(M) set for individuals with (genetic) ID ((G)ID) is therefore both timely and crucial to advance care, support shared decision-making, enable longitudinal monitoring, and facilitate health policy development. Its relevance extends to clinical research as well, particularly in rare diseases where trials face small sample sizes and heterogeneity. Regulators like the EMA and FDA increasingly require validated, well-justified PROMs tailored to the population under study.

During this talk, dr. Lotte Haverman will address the pressing need for conceptual clarity and standardization in PRO(M)s for (G)ID. By integrating patient and caregiver perspectives, and aligning with regulatory and methodological standards, we hope to contribute to more meaningful, person-centred outcome assessment across care, research, and policy. The first steps we have taken in developing a PRO(M) set for GID gave valuable insights, and we are now applying these understandings to PRO(M) set development for syndromes such as Noonan and Tuberous Sclerosis Complex (TSC).

Keywords: Patient Reported Outcomes (PROs), Patient Reported Outcomes Measures (PROMs), Patient centered care, Individuals with (genetic) ID, Generic

26. Factors That Impact Short and Medium Term Stability on Clinical Trial Measures in Children with Autism

Presenting Author: Sara Jane Webb

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Background: The Autism Biomarkers Consortium for Clinical Trials (ABC-CT) is a naturalistic longitudinal study of 6- 11 year olds with ASD. Measures were selected based on their use in prior clinical trials in autistic and NDD youth. The design of the ABC-CT allows the investigation of child and family factors that may impact measurement stability.

Methods: We include $N=268$ participants M age=8.54yrs (SD 1.64) with data at T1 and T2 (M T2-T1=+41.53days SD 9.43), or T3 (M T3-T1=+165.61days SD 10.11). The Aberrant Behavior Checklist (ABC) and the Autism Impact Measure (AIM) were included. In Aim 1, we used intraclass correlations (ICC) to test stability from T1-T2 and T1-T3. For Aim 2, we used stepped regression models to predict outcome behaviour (T2 or T3 score), including T1 behavioural score, child age, sex, race/ethnicity, family income, parental education; and child autistic behaviours and IQ.

Results: T1-T2 stability for the ABC and AIM subdomains were good ($ICCs=0.596-0.813$); T1-T3 was similar ($ICCs=0.568-0.776$). Only family income showed a consistent impact on scores, with parents with less income rating their children as having greater symptoms, frequency, and impact (10/17 models, $F_s>9.0$, $p_s<.01$). Short-term stability on the ABC irritability and lethargy was impacted by child demographic and family factors ($F>75.6$, $p_s<.001$, F Change $p_s\leq.05$). That is, parents with higher income were more likely to report decreases in severity of behaviours over time.

Conclusion: Commonly used clinical-trial measures showed good stability over both 6 weeks and 6 months. Scores at baseline and stability of the ABC over time were influenced by parent socio-economic status. Additional analyses will assess if families with higher income were more likely to change interventions during the study.

Keywords: Clinical trial measures, stability, ASD, parent socio-economic status, predictors

27. Psychometric Properties of the Clinical Anxiety Screen for People with Severe to Profound Intellectual Disabilities and its Application to Cross-Syndrome Research

Presenting Author: Jane Waite

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Background: Despite evidence of high rates of anxiety in individuals with neurodevelopmental conditions and severe and profound intellectual disability (ID), few valid tools exist to assess anxiety in this population. We have developed a new parent-report measure to address this gap—the Clinical Anxiety Scale for People with Intellectual Disabilities (CIASP-ID). The aim of this project was to evaluate the psychometric properties of the CIASP-ID and explore anxiety levels across genetic syndromes associated with ID.

Methods: In total, 308 participants with various neurodevelopmental conditions were recruited to the first study and completed a battery of questionnaires including the CIASP-ID. Test-retest reliability (TRR) and inter-rater reliability (IRR) data were available for 78 and 20 participants respectively. Data from this study was used to conduct an exploratory factor analysis (EFA) and investigate psychometric properties of the measure. A second sample of 394 participants completed the CIASP-ID as part of a multi-site study investigating outcomes in neurodevelopmental conditions. Data from the second study is used for confirmatory factor analysis (CFA) and cross-syndrome comparisons.

Results: The EFA indicated a four-factor structure encompassing anxiety, pain, low energy/withdrawal and consolability. The anxiety, pain and low energy/withdrawal subscales had robust psychometric properties ($\alpha=.81-.92$, TRR=.79-.88, IRR=.64-.71). The CFA supported a three-factor model omitting the consolability subscale. Preliminary cross-syndrome analyses comparing 10 syndromes identified cross syndromes differences, including elevated anxiety in Wiedemann-Steiner syndrome and fragile x syndrome compared to other rare genetic syndromes including Kleefstra syndrome and Rubinstein-Taybi syndrome ($p \leq .005$). Cross syndrome risk factors for anxiety will also be presented.

Conclusion: The CIASP-ID appears to be a reliable and valid tool for research with people with rare genetic syndromes. Cross-syndrome comparisons are vital for identifying additional groups at high risk of anxiety. This talk will present detailed syndrome-level data, offering new insights to inform tailored assessment and intervention.

Keywords: Intellectual Disability, Neurodevelopmental Conditions, Anxiety, Mental Health, Measure Development, Rare Genetic Syndromes

28. An Investigation of Autonomic Function in SYNGAP1-Related Intellectual Disability

Presenting Authors: Sydni Weissgold

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Background: Dysregulation of the autonomic nervous system may play a role in the presence of behaviours that challenge. This relationship is particularly relevant in SYNGAP1-related intellectual disability (ID), a non-inherited ID in which behaviours such as physical aggression and self-injury are commonly reported.

Methods: To investigate autonomic function in SYNGAP1, we recruited 21 individuals with SYNGAP1 and 15 typically developing controls (TDC) to measure autonomic function via heart rate variability (HRV) analysis. An electrocardiogram (ECG) recording was collected while participants watched a 20-minute film-based paradigm with baseline, calming and arousing blocks. Analysis of the ECG was conducted using HeartPy, where time-domain and frequency-domain HRV metrics were calculated for each block. Aligned rank transformation ANOVAs were conducted where HRV metrics were compared by group (SYNGAP1 vs TDC).

Results: Between group differences were apparent across all three conditions when examining beats per minute (BPM) ($F(1, 31) = 15.40, p < 0.001$), as well as traditional HRV metrics, such as time domain (pNN50: $F(1, 31) = 7.04, p = 0.01$) and frequency domain (high-frequency: $F(1, 31) = 5.79, p = 0.02$) measures. BPM was higher in the SYNGAP1 group when compared to TDC, while the pNN50 and high-frequency measures, which are both influenced by parasympathetic tone, were lower in the SYNGAP1 group, compared to TDC. Additional time- and frequency-domain measures were assessed (i.e. RMSSD, SDNN, very-low-frequency, and low-frequency), in which differences between groups approached significance in some metrics (RMSSD, very-low-frequency) and were not different between groups in other measures (SDNN, low-frequency). Between condition differences were observed in certain metrics, including RMSSD, SDNN, pNN50 and high-frequency; all measures were higher during the calming condition in both groups. There were no significant group by condition interactions.

Conclusion: These results demonstrate a decrease in parasympathetic tone in individuals with SYNGAP1-related ID compared to TDC, which may contribute to increased levels of distress.

Keywords: SYNGAP1, intellectual disability, autonomic function

29. THE LECLEZIO – DE VRIES PRIZE: Feasibility and Acceptability of the TAND Toolkit App

Presenting Author: Tosca-Marie Heunis

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Background: Tuberous Sclerosis Complex (TSC) Associated Neuropsychiatric Disorders (TAND) significantly impact the lives of families living with TSC, yet are often not identified or managed. To address this, we developed the 'TAND Toolkit App' in partnership with families, containing a self-report quantified TAND Checklist (TAND-SQ) and a TAND toolkit to help families identify 'what to seek' from professionals and 'what to do' tips and strategies that they can implement at home. This study aimed to evaluate the feasibility and acceptability of this TAND Toolkit App.

Methods: The app and the TAND toolkit were initially developed separately. The TAND consortium, and individuals with TSC and caregivers from Boston Children's Hospital, Cincinnati Children's Hospital, the TSC Alliance and TSCi, evaluated the app and toolkit at various stages of development. After incorporating their feedback, the app and toolkit were integrated, and evaluated by participants from the Belgian (be-TSC) and Dutch (STSN) TSC family support organisations.

Results: In total, 44 app feedback forms, 56 toolkit feedback forms, and two focus groups (n=36) were completed, across all stages of testing. Forty users used a smartphone, and four a tablet/iPad; 29/44 were iOS users. The majority (40/44) rated the language in the app as easy to understand, liked the app user interface, and found the steps for progressing through the app logical, with an overall app rating of 91% (40/44). Most rated the TAND toolkit as 'helpful' or 'very helpful' with an overall acceptability rating of 86% (48/56). The majority of be-TSC and STSN families (15/20) gave the integrated TAND Toolkit App a 4- or 5-star rating. Families expressed the need for multilingual functionality, and the ability to use the app on a computer.

Conclusion: The TAND Toolkit App is a feasible and acceptable mobile-health resource for families and individuals with TSC, with scope for improvements.

Keywords: Tuberous Sclerosis Complex, TSC-Associated Neuropsychiatric Disorders, TAND Toolkit App, Feasibility, Mobile-health, TANDem

30. KEYNOTE: Human iPSC-Based Disease Models for Personalized Therapeutics in Neurodevelopmental Disorders

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Human induced pluripotent stem cell (hiPSC) technology enables the creation of patient-specific cellular models that capture the genetic and phenotypic complexity of neurodevelopmental disorders. Our research leverages hiPSC-derived 2D and 3D neural cultures—including brain organoids—to explore cellular and network-level dysfunctions, with a particular focus on neuron-glia interactions. These systems provide a powerful platform to uncover disease mechanisms across a spectrum of rare conditions, such as GRINopathies, autism spectrum disorders, and white matter disorders.

We collaborate closely with clinical partners to ensure translational relevance, validating in vitro phenotypes against clinical presentations. By integrating advanced imaging, electrophysiological recordings, and multi-OMICs approaches, we aim to identify biomarkers and therapeutic targets that are both human-relevant and personalized. This presentation will highlight how patient-specific iPSC models are advancing precision medicine strategies, offering new hope for tailored interventions in rare neurodevelopmental disorders.

Keywords: Human induced pluripotent stem cells (hiPSC); Neurodevelopmental disorders; Patient-specific models; Neuron-glia interactions

31. Impact of Infant Testosterone Treatment on Neurodevelopment in Boys with 47,XXY

Presenting Author: Shanlee Davis

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Background: Prenatal identification of 47,XXY / Klinefelter syndrome is increasing, prompting interest in proactive interventions for associated neurodevelopmental deficits. Infant testosterone treatment has been proposed to improve neurodevelopment in 47,XXY, but supporting evidence is limited. This study tested whether early testosterone treatment improves neurodevelopmental outcomes in the preschool years.

Methods: The eXtraordinary Babies Study prospectively follows boys with prenatally identified 47,XXY, beginning in infancy, with annual developmental assessments. Two-thirds of participants received testosterone (25 mg IM every 4 weeks for 3 doses) within the first year, either via clinical trial (NCT03325647) or clinical care. Development was assessed at 12, 24, and 36 months using the Bayley Scales of Infant Development – 3 (BSID3) and adaptive function via parent-completed Vineland Adaptive Behavior Scales – 3 (VABS3) annually through 60 months of age. Parental cognition was measured using the NIH Toolbox. Mixed-effects linear regression was used to assess whether testosterone predicted neurodevelopmental outcomes, adjusting for confounders including parental cognition, breastfeeding, and socioeconomic status.

Results: Of 160 participants, 105 (66%) received testosterone. Treated participants had higher socioeconomic status, greater likelihood of breastfeeding, and higher parental cognitive scores. In unadjusted analyses, testosterone-treated infants had slightly higher BSID3 Cognitive Composite scores at 12 months (103±9 vs 99±9, $p=0.03$); however, no other differences were observed at any timepoint. In adjusted models, testosterone was not a significant predictor of any BSID3 or VABS3 scores. Developmental trajectories over time also did not differ by treatment group.

Conclusion: Infant testosterone treatment in 47,XXY does not significantly impact early neurodevelopment or adaptive function. Previously reported benefits may reflect confounding by other genetic, sociodemographic and early life exposures. Longitudinal follow-up is ongoing to determine whether differences emerge later.

Keywords: Klinefelter syndrome, sex chromosome aneuploidy, testosterone, hormones, neurodevelopment

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32. Controlled Trial of Metformin in Fragile X Syndrome

Presenting Author: Randi Hagerman

Hagerman R.¹, Bolduc F.², Lippe S.³, Martin C.-O.³, Jacquemont S.³, Hessler D.⁴, Abbeduto L.⁴, Santos E.⁵, Biag H.M.B.⁵, Schneider A.¹, Thurman A.J.⁵, Tassone F.⁶, Hagerman P.⁶, Ponzini M.⁷, Kim K.⁸

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Background: In Fragile X syndrome (FXS) the absence or deficiency of FMRP leads to dysregulation of the insulin signalling and the mTOR pathway. Preclinical animal model testing as well as case studies in FXS patients showed ability of metformin to improve cognitive and behavioural deficits seen in FXS.

Methods: A multi-site randomized controlled trial (RCT) of oral metformin in FXS (dosing up to 500 mg bid) lasting 4 months took place at the MIND Institute, University of Alberta, and Université de Montréal to assess the benefits of metformin in the treatment of language deficits (primary) and behaviour problems. Enrolment included 118 participants (88% male) between the ages of 6 and 35 (14.9±7.3 yrs). Participants were randomized to metformin or placebo and completed visits at baseline, 2 months, and 4 months. Efficacy analyses were performed for short-term (2-month) and long-term (4-month) benefit of metformin, adjusted for age, sex, IQ, and study site.

Results: We found long-term language improvement in the metformin group compared to the placebo (4-month change = 3.07±2.5 vs. -0.43±2.5) although statistically insignificant (p=0.297). The ABCFX demonstrated significant benefits of 4-month metformin on the Socially Unresponsive/Lethargic scale (mean change difference = -1.59±0.7, p=0.022), and the ABC Composite Score (-6.72±2.8, p=0.016). We found significant short-term (2-month) benefits with metformin for the irritability, stereotype, and hyperactivity (p<0.05). The ADAMS depressed mood and general anxiety total scores showed significant short-term benefits with metformin (p<0.05). The Peds QL emotional functioning showed significant short-term benefit with metformin (difference = 4.94±2.45, p=0.044).

Conclusion: This RCT of metformin in children (6 and older) and adults with FXS generally demonstrated improvement in behaviour and this is consistent with clinical observations in FXS. It supports that metformin is a targeted treatment for FXS behaviour symptoms and can be recommended clinically.

Keywords: Fragile X syndrome, Treatment, metformin, controlled trial, behaviour benefits

33. Evaluation of the Effect of Intranasal Insulin on Development and Behaviour in Phelan-McDermid Syndrome

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Background: Phelan-McDermid syndrome (PMS) is a rare neurodevelopmental disorder caused by a deletion or mutation of the SHANK3 gene, characterised by severe to profound developmental and speech delay and autism, and starting at adolescence, mood disorders and regression. Studies in cell and animal models have demonstrated that insulin and related molecules such as insulin-like growth factor 1 (IGF1) can enhance synaptic plasticity and cognitive function. A pilot study suggested individuals with PMS may benefit from intranasally administered insulin (INI), but this need to be confirmed in a fully powered trial. To deliver data on efficacy of INI on improving cognitive development in people with PMS, we aim to conduct a larger well-powered clinical trial in the UK, where the treatment is not currently available.

Methods: Two-parallel group, single-centre, double-blinded placebo-controlled RCT over 12 months with 2:1 randomisation in individuals with PMS aged 3-18 years (n=105) with an open label extension to evaluate the efficacy and safety of INI on cognitive development in children and young adults with PMS. Longer term outcomes will be evaluated in individuals already treated with INI at participating sites in Europe. Primary outcome measure will be the Bayley Scales of Infant and Toddler Development v4. Secondary measures include adaptive behaviour (Vineland3), social initiation behaviour (Parent-Child Interaction - PCI), sensory sensitivity (Short Sensory Profile); Clinician's Global Impression – Improvement; health-related quality of life and caregiver burden. To determine the predictors of response and effect on mental health and behavioural outcomes in people being treated with INI, we will be using trial data alongside observational data from clinics in Europe.

Results: The planned protocol and recruitment strategy for the treatment trial will be presented.

Conclusion: The issues that determined our trial design and recruitment strategy may be relevant to other rare neurodevelopmental conditions.

Keywords: Phelan McDermid syndrome, Shank3, Randomised trial, Insulin

34. Bridging Genetic Bridges: Unravelling E/I Imbalance to Unlock Personalized Treatments in Monogenetic Disorders

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Background: The study of monogenetic disorders affecting child development can lead to personalized treatment options. However, focusing on individual conditions has created gaps in knowledge about shared clinical manifestations like developmental delays, seizures, and motor deficits. A common underlying mechanism in these disorders is the disruption of excitatory (E) and inhibitory (I) signaling. While current pharmacological treatments aim to address E/I balance, issues such as inadequate responses or adverse reactions are frequent and poorly understood. Thus, there is a significant need for reliable technology to measure E/I ratios in clinical contexts.

Methods: To fill this gap, we developed an EEG-based E/I marker based on our "critical oscillations" (CROS) computational model. This model characterizes E/I balance as an emergent property of neuronal circuits, defined by their high spatio-temporal complexity. By simulating various parameters of E/I, we elucidated how optimal E/I states support both local and global information processing. This framework allowed us to create an algorithm for extracting functional network E/I (fE/I) from EEG oscillations.

Results: We present data on EEG-based E/I characterization from cohorts with monogenetic conditions, including Grin2B disorder, STXBP1 deficiency, Kleefstra syndrome and Tuberous Sclerosis Complex. Our results indicate that different genetic alterations may lead to similar clinical outcomes through shared E/I disruptions. Additionally, we provide proof-of-principle for testing E/I-altering compounds like Bumetanide and L-serine through randomized controlled trials (RCTs) and n-of-1 trials, demonstrating their potential in tracking E/I dynamics. By combining EEG biomarker evaluation with machine learning analysis, we developed treatment prediction models tailored for individuals with ASD and other monogenetic disorders.

Conclusion: Our research highlights both commonalities and differences in E/I dynamics across genetic disorders, suggesting shared disruptions can produce similar clinical presentations. This work enhances our understanding of neurodevelopmental variability and contributes to developing more effective treatment strategies for affected children.

Keywords: Monogenetic conditions, E/I balance, personalized treatment

35. Proteomic Profiles Related to Neurodevelopmental Copy Number Variant Carriers in UK Biobank Open New Insights into Internalising and Cardiometabolic Multimorbidity

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Background: Multimorbidity, the presence of two or more concurrent chronic conditions within an individual, represents a current and future major public health concern. People with Copy Number Variants associated with high risk of neurodevelopmental conditions (ND-CNV) have increased risk of multimorbidity of internalising disorders and cardiometabolic conditions (ICM-MM), but the reasons remain unclear. We explored associations between proteomic profiles and ND-CNV status in older-age individuals to increase understanding of ICM-MM risk.

Methods: Olink data on 2,920 proteins were available for 49,202 individuals (mean age 56.8) within the population-based UK Biobank cohort (845 with ND-CNV and 48357 without). Diagnosis of ICM-MM was made using primary care and hospital records. Logistic regression was performed to predict ICM-MM status with protein and ND-CNV genotype as well as their interaction (to test if ND-CNV modifies the association between ICM-MM and protein level). We evaluated associations with ND-CNV deletions only, duplications only, as well as individual ND-CNVs present in >10 individuals. Covariates included demographic and lifestyle factors, including body mass index. In significantly associated proteins, STRING was used to assess protein-protein interaction, and gene set analysis was performed using Gene Ontology (GO) gene sets.

Results: Significant ND-CNV*protein interactions were found with deletions (N=22), duplications (N=88), TARdup (N=69), 15q11.2del (N=59), and dup (N=50), 16p12.1del (N=8), 16p13.11del (N=13) and dup (N=64) and 22q11.2dup (N=14). Protein-protein interactions were found for duplications in STRING (duplications only [p=0.0009], TARdup [p=2.42x10⁻⁹], 16p13.11dup [p=0.0014]) and one deletion (15q11.2del [p=0.011]). Duplications only and TARdup were the only ND-CNVs to show enrichment in GO gene sets and were related to metabolic, catabolic, and erad pathways.

Conclusion: Examination of proteomic profiles may provide insights into associations between ND-CNV status and risk of physical and mental health multimorbidity in older age. Diagnosis of ICM-MM may be associated with altered metabolic and catabolic pathways in individuals with duplications, in particular.

Keywords: Internalising, Cardiometabolic, CNV, Proteomics, Multimorbidity, UK Biobank

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36. P70 S6 Kinase as a Potential Peripheral Biomarker for 16p11.2 Copy Number Variant- Associated Neurodevelopmental Syndromes

Presenting Author: Riccardo Brambilla

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Background: Copy number variants (CNVs) at the 16p11.2 chromosomal locus, including deletions (DEL) and duplications (DUP), are strongly associated with autism spectrum disorder (ASD), intellectual disability, attentional deficits, epilepsy, and psychiatric comorbidities. The 16p11.2 locus encompasses 27 genes, including MAPK3/ERK1, a key component of ERK pathway. Currently, diagnosis of 16p11.2 CNV-associated syndromes relies on behavioural and psychiatric evaluations, which are complicated by the heterogeneity and variable penetrance of phenotypes, hence the need of novel biomarkers to support diagnosis and prognosis. In this study, we aimed to: i) evaluate the impact of 16p11.2 CNVs on behavioural phenotypes; ii) correlate signalling proteins' alterations in patient-derived peripheral blood mononuclear cells (PBMCs) with specific behavioural phenotypes.

Methods: Psychiatric, cognitive, and neurodevelopmental presentations were assessed in 110 young people (41 with 16p11.2 deletion, 32 with duplication, and 37 unaffected siblings). Proteins were extracted from patients- and healthy siblings-derived PBMCs and subjected to automated Western blot analysis. The levels of signalling proteins along ERK and mTOR pathways were measured.

Results: 16p11.2 DEL and DUP carriers exhibited significantly higher symptom counts for Anxiety, Attention Deficit Hyperactivity Disorder (ADHD), Developmental Coordination Disorder (DCD) and autism traits. DUP carriers also demonstrated significantly increased symptoms for Oppositional Defiant Disorder (ODD) and Mood Disorder. Both DEL and DUP carriers displayed lower Full-Scale IQ. Our molecular analysis on PBMCs revealed reduced levels of p70 S6 kinase (p70S6K), a key effector of the mTOR pathway and a crucial player in protein synthesis, in both DEL and DUP carriers. Notably, p70S6K levels inversely correlate with ASD severity.

Conclusion: This study underscores the significant impact of 16p11.2 DEL and DUP on psychiatric, cognitive, and neurodevelopmental outcomes in young people. In addition, p70S6K in PBMCs may help understanding the psychopathological mechanisms and possibly serve in the future as novel biomarker for 16p11.2 CNV- associated syndromes.

Keywords: 16p11.2 copy number variants, neurodevelopmental syndromes, ERK and mTor pathways, p70 S6 kinase; peripheral biomarker

37. Effects of Metformin Versus Placebo on Children with Fragile X Syndrome: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Presenting Author: Yiting Zhu (Corresponding author: Xu Q)

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Background: Fragile X syndrome (FXS) is a monogenic disorder caused by excessive CGG trinucleotide repeat expansions (>200 repeats) in the 5' untranslated region of the *FMR1* gene, leading to hypermethylation, gene silencing, and subsequent loss of Fragile X Messenger Ribonucleoprotein 1 (FMRP). FMRP deficiency enhances mRNA translation and activates two key protein synthesis pathways: mTOR and MAPK/ERK. Metformin has been shown to inhibit mTORC1 activity and MAPK signalling. Recent studies reported behavioural and cognitive improvements in FXS drosophila and mouse models with metformin treatment, while preliminary clinical data in FXS patients also demonstrated favourable behavioural and cognitive outcomes.

Methods: We recruited children aged 2-16 years with genetically confirmed FXS, BMI >3rd percentile, and taking ≤2 medications at the Children's Hospital of Fudan University. A block randomization method was employed, with 4 participants per block randomized 1:1 to the metformin or placebo group. Adverse events were monitored every 2 months, and outcomes were assessed at 6 months post-treatment. Blinding was maintained for investigators, participants, outcome assessors, and statisticians. Primary outcome was the Aberrant Behavior Checklist (ABC), with secondary outcomes including Griffiths Developmental Scales, ADOS-2, Sleep Questionnaire, Repetitive Behavior Scale-Revised (RBS-R), Clinical Global Impression (CGI).

Results: Between January 1, 2022, and January 1, 2025, 34 eligible participants were enrolled, with 4 withdrawals. Fifteen participants each were allocated to the metformin and placebo groups. Baseline characteristics were comparable between groups. At 6 months, metformin showed significantly greater improvements in ABC-hyperactivity subscale (metformin: -7.86 ± 6.97 vs. placebo: -0.80 ± 8.09 ; $t = -2.562$, $p = 0.016$), bedtime resistance (metformin: 0.00 ± 1.64 vs. placebo: 2.46 ± 2.50 ; $t = -3.188$, $p = 0.004$), and overall sleep quality (metformin: -0.73 ± 5.14 vs. placebo: 5.13 ± 6.85 ; $t = -2.651$, $p = 0.013$). Metformin exhibited a non-significant trend toward improvement in gross motor function (metformin: 3.80 ± 2.66 vs. placebo: 1.86 ± 4.10 ; $t = 1.208$, $p = 0.244$). Two metformin-treated participants reported transient appetite loss and weight reduction ($p = 0.483$).

Conclusion: Metformin may ameliorate hyperactivity and sleep disturbances in children with FXS, with a potential trend toward motor improvement. The favourable safety profile supports further investigation of metformin as a targeted therapy for FXS.

Keywords: Fragile X Syndrome; Metformin; mTOR Signalling Pathway; Behavioural Symptoms; Randomized Controlled Trial

38. Parents' and Healthcare Professionals' Experiences in Interprofessional Collaboration in Rare Genetic Intellectual Disability Syndrome: A Qualitative Study into Barriers and Facilitators

Presenting Author: Mana Nasori

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Background: People with rare genetic intellectual disability syndromes (RGIDS) have physical and mental health related problems, with a high risk for challenging behaviour (e.g. aggression, self-injury). They rely on integrated and specialized expertise of numerous healthcare professionals across medical care, intellectual disability (ID) care, mental care and social care. Additionally, parents are often experts in their child's genetic syndrome, health and behaviour, and play a key role in interacting with and connecting professionals involved in their child's care. However, interprofessional collaboration with parents and healthcare professionals is challenging. In daily practice, professionals often work in silos, with limited communication and lack of coordination in care. While medical issues and genetic diagnosis receive primary attention, parents frequently experience a gap in behavioural care. Consequently, parents often find themselves taking on a professional role, which may not always be within their capabilities. Underscoring the need for improved interprofessional collaboration. This study explored the barriers and facilitators experienced by parents and healthcare professionals in interprofessional collaboration.

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

Results: The results will outline the barriers and facilitators experienced by parents and healthcare professionals in interprofessional collaboration. As the interviews are currently being conducted and require analysis, the findings are expected to be presented in September 2025.

Conclusion: By understanding the barriers and facilitators in interprofessional collaboration (with parents in an expert role), we expect to identify areas for improvement and unravel professional competences to enhance interprofessional collaboration and address what is needed to adequately service and treat families of RGIDS people. This study is designed to hopefully unburden parents, allowing them to collaborate more as experts in their child's care.

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

39. Elucidating Interactions Between Attentional Control and Socially Oriented Attention in Young Children with Neurofibromatosis Type 1

Presenting Author: Darren Hocking

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Background: Reduced visual engagement to socially enriched stimuli and atypical response to joint attention are core features in autism spectrum disorder (ASD), but there is a dearth of research in children with neurofibromatosis type 1 (NF1). We aimed to examine commonalities and syndrome-specific differences in preferential attention to social stimuli and response to joint attention in preschoolers with NF1, chronologically age-matched children with non-syndromic autism, and typically developing (TD) controls.

Methods: This study employed a prospective cross-sectional design using novel eye-tracking paradigms to evaluate various aspects of participant eye gaze during passive viewing of videos containing both social and non-social information, or towards objects that were either gazed-at (congruent object) or not gazed-at (incongruent object) by an unfamiliar adult (joint attention). Another paradigm examined duration of time looking at a cartoon video clip as a measure of sustained attention.

Results: The sample comprised 25 children with NF1 (mean age 54.1 months, SD = 8.9), 25 children with non-syndromic autism (mean age 49.9 months, SD = 9.7), and 20 TD controls (mean age 51.2 months, SD = 12.2). After controlling for differences in cognitive ability, both children with NF1 and non-syndromic autism showed a lack of preferential attention towards social stimuli, an opposing pattern to that seen in TD controls. Children with NF1 and non-syndromic autism were less likely to establish joint attention, but with more time the NF1 group were comparable to TD controls. In the NF1 group, slower times to first fixation to social stimuli were associated with elevated autistic traits and poorer social adaptive functioning.

Conclusion: The current findings build upon previous evidence in school-aged children with NF1 and suggest young children with NF1 might miss salient social information thereby reducing their social learning opportunities. This may have important implications for early interventions such as attention training programmes aimed at improving social attention skills in NF1.

Keywords: Neurofibromatosis type 1; eye-tracking; social attention; joint attention; Autism; sustained attention

40. Resting State EEG Power and Connectivity in SYNGAP1-Related Disorder

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Background: SYNGAP1-related disorder is a genetic condition caused by a pathogenic variant in the *SYNGAP1* gene. Individuals with this disorder frequently present with intellectual disability, autism spectrum disorder, and other behavioural challenges. Resting-state electroencephalography (EEG) provides a window into neural oscillatory activity and may help identify biomarkers for future clinical trials and targets for intervention. However, few EEG studies have been conducted to date on the neuronal activity of individuals with SYNGAP1-related disorder.

Methods: We collected resting-state EEG data from 17 individuals with SYNGAP1-related disorder and 27 typically developing controls. Differences in resting-state activity were examined in terms of relative band power (delta: 1–4 Hz; theta: 4–8 Hz; alpha: 8–12 Hz; beta: 13–30 Hz; and gamma: 30–45 Hz), functional connectivity, and peak alpha frequency. Functional connectivity was calculated using the debiased phase lag index, which quantifies asymmetry in phase differences between EEG signals. Peak alpha frequency was defined as the frequency at which alpha oscillations attained maximum power.

Results: We found that individuals with SYNGAP1-related disorder showed reduced relative alpha power across all regions (frontal, central, temporal, and parietal-occipital) compared with typically developing controls. Relative delta power was elevated in the central and parietal-occipital regions, while relative beta power was reduced only in the parietal-occipital areas. Peak alpha frequency was also reduced in individuals with SYNGAP1-related disorder compared with controls. No differences in functional connectivity were observed between the two groups.

Conclusion: Overall, these results shed light on the possible neural oscillatory impairments in those with SYNGAP1-related disorder. These findings may support the potential of neuronal activity alterations as a valuable biomarker in this population

Keywords: SYNGAP1-related disorder, EEG, Neural oscillations

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41. Age-Varying Distinct Neuroanatomy in Young Children with Autism Spectrum Disorder and Fragile X Syndrome

Presenting Author: Danyong Feng

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Background: Autism spectrum disorder (ASD) is commonly associated with fragile X syndrome (FXS), yet their neurobiological underpinnings may differ. This study aimed to identify the neuroanatomical profiles and the age effects on brain's developing trajectories that might be distinct or shared in FXS and idiopathic ASD.

Methods: We recruited 190 children: 46 with FXS (5.39 ± 2.68 years), 90 with idiopathic ASD (3.38 ± 1.36 years), and 54 typically developing (TD) children (5.40 ± 2.90 years). T1-weighted structural MRI scans were acquired using a GE 3T Discovery MR750 system. Age-varying, voxel-based morphometry (VBM) was conducted. Statistical analyses employed linear regression with age, gender, and total intracranial volume as covariates, with significance set at FWE-corrected $p < 0.05$. Regions of interest (ROIs) were defined based on VBM generated clusters and mean grey matter volumes (GMVs) of ROIs were extracted.

Results: The most pronounced neuroanatomical differences were observed in the FXS group. Children with FXS had increased GMV in subcortical regions and Crus I of the cerebellum, but decreased GMV in insular and other cerebellar regions compared to the ASD and TD groups. The ASD group showed increased GMV in bilateral temporal lobes and right insula compared to TD controls, though these differences were less pronounced than those in FXS. Children with ASD had significantly faster growth rates of morphological volumes than the other two groups.

Conclusion: Our findings suggest that FXS and ASD have distinct neuroanatomical signatures during early childhood, particularly in subcortical and cerebellar regions, which are associated with divergent developmental trajectories. We conclude that these two conditions have distinct neurobiological underpinnings at spatial and temporal scales, despite their overlapping clinical symptoms. These findings have important implications for diagnosis and targeted interventions for young children with FXS and ASD.

Keywords: Fragile X syndrome; Autism spectrum disorder; sMRI; Voxel-based morphometry; Social-impairment

42. Anxiolytic Effects of Riluzole in 22q11.2 Deletion Syndrome

Presenting Author: Claudia Vingerhoets

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Background: 22q11.2 deletion syndrome (22q11DS) is associated with an increased risk of developing a variety of psychiatric disorders, including anxiety and psychotic disorders, and cognitive dysfunction. Genetically mediated alterations in glutamate and GABA, and consequential disruption of the excitation/inhibition balance, are implicated in the occurrence of psychiatric and cognitive symptoms in 22q11.2DS. Previously we reported that a single dose of riluzole, a glutamate and GABA modulating compound, numerically decreased glutamate concentrations in the anterior cingulate cortex (ACC). Here, we examined the effects of riluzole treatment on psychiatric symptoms and cognitive functioning.

Methods: This study had a placebo-controlled, partially blinded fixed order cross-over design. Twenty-nine participants (10 male, 19 female) completed the study (mean age 30.6 years). All participants received 8-week treatment with placebo and 8-weeks of oral riluzole treatment (100 mg daily), preceded by a baseline measurement of psychiatric symptoms and cognition. After both interventions, participants underwent an assessment of psychiatric symptoms, as well as assessment of ACC glutamate and GABA levels using ¹H-MRS. The Subjective wellbeing Scale (SWN), Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression (CGI), and State-Trait Anxiety Inventory (STAI) were administered to assess clinical symptoms. All assessments were conducted by a trained research assistant who was blind to the order of the interventions.

Results: After riluzole, significant improvement was found in anxiety on the generalized psychopathology (PANSS) scale ($p < 0.01$). Effects were stronger in women and participants with a CGI score of ≥ 6 . GABA concentrations correlated significantly with SWN scores after riluzole ($p < 0.005$), but not after placebo. Similarly, GABA concentrations were inversely correlated with anxiety after riluzole ($p < 0.006$, STAI), but not after placebo. Riluzole did not significantly alter ACC glutamate and GABA concentrations.

Conclusion: The current results suggest that riluzole may improve anxiety in 22q11.2DS. Therefore, glutamate and GABA may be suitable treatment targets.

Keywords: 22q11 deletion syndrome, riluzole, anxiety, glutamate, GABA

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43. An N-of-1 Trial of Fluoxetine in KCNC1 Related Disorder

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Background: KCNC1 related disorder is an ultra-rare neurologic and developmental disorder caused by a genetic variant in a potassium channel subunit (Kv3.1). Gain of function variants in Kv3.1 can cause significant motor and cognitive delays, and hypotonia. Fluoxetine has inhibitory effects on the Kv3.1 subunit. The objective of this study was to evaluate the safety and effectiveness of fluoxetine to treat motor delays in a child with KCNC1 related disorder and a gain-of-function variant in.

Methods: A randomized, double-blind, withdrawal-reversal ABA-phase design trial of fluoxetine was conducted in a 3-year-old child over 40 weeks. The primary outcomes were motor development assessed weekly on the Early Motor Questionnaire (EMQ) and safety as per adverse event reporting. Data were analysed through Bayesian interrupted time-series (ITS), with flat priors.

Results: The participant attended all trial visits and completed all endpoints. In the ITS model, time was associated with a 0.52 points per week gain on the EMQ (95% credible interval 0.28 to 0.91). Treatment with fluoxetine was associated with a 6.61 point gain on the EMQ, which approached significance (95% CrI -0.53 to 14.78). The treatment was well tolerated, but withdrawal irritability emerged during the second placebo phase.

Conclusion: Fluoxetine may support motor development for young children with KCNC1-related disorder and gain of function variants. Rigorous individualized clinical research in rare genetic conditions will be essential for building treatment evidence to guide care.

Keywords: N-of-1, KCNC1, clinical trial, motor development

44. TANDem-2: Closing the Gap to Interventions for TAND – Study Protocol

Presenting Author: Lucas Gabriel Gutiérrez Lafrentz

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Background: TSC-Associated Neuropsychiatric Disorders (TAND) significantly affect individuals and families. Despite increasing awareness, there is a lack of large-scale longitudinal data on TAND severity trajectories and their predictors. Moreover, little is known about the relationship between caregiver wellbeing and TAND severity, and no interventions to support caregiver wellbeing have been evaluated in TSC to date. TANDem-2 addresses these gaps by (1) mapping TAND severity and its potential predictors over time, (2) examining the association between caregiver wellbeing and TAND severity, and (3) evaluating whether an ultra-brief online caregiver support programme can improve caregiver wellbeing.

Methods: For Aims 1 and 2, data will be collected via the TAND Toolkit App from 500 individuals with TSC or their caregivers. Accelerated longitudinal data will be collected at five time points over 12 months. Data will include individual characteristics (e.g., age, sex, genotype, seizure history, intellectual ability, current treatments), caregiver characteristics (e.g., age, relationship, burden, wellbeing), and TAND severity measures (TAND-SQ). Latent class mixed modelling will identify distinct TAND severity trajectories, while multinomial logistic regression will examine predictors of these trajectories. Structural equation modelling and longitudinal mediation analyses will explore the relationship between caregiver wellbeing and TAND severity. For Aim 3, participatory methods with the TAND Consortium will be used to adapt a 3-session online wellbeing programme for the TSC community, followed by an online pilot clinical trial.

Results and Conclusions: Identifying TAND severity trajectories and predictors will inform prognosis, mechanisms, and treatment, and support clinical trial readiness using the TAND-SQ as a potential outcome measure. Understanding caregiver wellbeing may shift clinical practice towards more inclusive interventions. Testing the feasibility of a scalable online caregiver programme will offer preliminary evidence for larger trials and potentially provide an accessible tool to support families.

Keywords: Tuberous Sclerosis Complex; TSC-Associated Neuropsychiatric Disorders; TAND; TAND-SQ Checklist; TANDem; TAND Toolkit App

45. KEYNOTE: Improving Care for People with Rare Genetic Variants Associated with Neurodevelopmental Conditions: Contributions Large Longitudinal Research Cohorts Can Make

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Background: A number of Copy Number Variants are associated with high risk of neurodevelopmental conditions (ND-CNVs) as well as a range of physical and mental health difficulties. ND-CNVs tend to be diagnosed early in life, offering opportunities for timely intervention and reduced risk of chronic manifestations down the line. Unfortunately, such opportunities are often missed. Large longitudinal research cohorts can make important contributions towards improving care.

Methods: Findings are presented from the Cardiff clinical genotype-first ECHO cohort and two population-based UK cohorts. ECHO comprises >3,000 individuals with a range of rare mutations and their unaffected (control) siblings and parents. Detailed, wide-ranging longitudinal phenotyping is conducted as well as brain imaging studies. Biological samples are collected for genotyping and protein and iPSC analysis. Population-based cohorts are BiB (Born in Bradford birth cohort; n~7500 genotyped, 2% with ND-CNV) and UKBB (UK Biobank; n~460,000 genotyped, 1.6% with ND-CNV).

Results: ECHO findings indicate high rates of psychiatric, neurological and other difficulties (e.g., sleep). Longitudinal analysis shows differences in neurodevelopmental and mental health trajectories in those at increased risk of psychosis. In older age (UKBB) ND-CNV increases risk of (co)-occurrence of physical and mental health conditions. Most children with ND-CNVs in BiB had not received a genetic diagnosis. Despite learning and behavioural difficulties in school, few received additional school support. Our multidisciplinary research is indicating brain dysconnectivity and signalling pathway disturbances contribute to vulnerabilities.

Conclusion: Large clinical and population-based research cohorts can contribute to improved care by: 1) documenting the issues individuals face and how these develop over time and identifying predictors that may aid early intervention; 2) being a hub for multidisciplinary research elucidating mechanisms underlying genotype-phenotype associations that may contribute to improved therapeutic interventions; 3) increasing awareness by disseminating findings widely, working closely together with affected families and different stakeholders.

Keywords: CNV, neurodevelopment, psychiatric, longitudinal, clinical cohort, population-based cohort

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Abstracts for Poster Presentation

(in alphabetical order)

POSTER 1: Adaptive Functioning, Behavioural Problems and Strength-Based Profiles in Children with Williams Syndrome

Presenting Author: Funda Akpınar

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Background: Williams syndrome is a rare neurodevelopmental disorder characterised by distinctive cognitive, behavioural, and adaptive functioning profiles. While cognitive impairments and sociability are well-described, few studies have simultaneously examined adaptive skills, behavioural problems, and family-reported strengths in a comprehensive manner. This study aimed to evaluate adaptive functioning and behavioural problems in children with Williams syndrome and to explore their most positively perceived traits as reported by families.

Methods: A total of 16 children (mean age: 6.5 years, range: 2–17; 56.3% female) with genetically confirmed Williams syndrome were assessed. Adaptive functioning was evaluated using the Vineland Adaptive Behaviour Scales-II, and behavioural problems were assessed with the Child Behavior Checklist (CBCL) 4–18. Parents were also asked to describe their child's most positive characteristics.

Results: The majority of participants showed significant delays in adaptive functioning, with 62.5% scoring below -2 SD on total adaptive composite scores. Subdomain analysis revealed severe impairments particularly in communication, daily living skills, and written expression. While most CBCL scales were within the normal range, attention problems (22.2% in clinical range) and aggressive behaviour (18.2% in clinical range) were noted as areas of concern. Positive traits reported by families included sociability, cheerfulness, kindness, and emotional warmth, with descriptors such as "cheerful", "loving", "compassionate", and "friendly" frequently mentioned.

Conclusion: Despite profound adaptive skill limitations, children with Williams syndrome often exhibit emotional warmth and social strengths as perceived by caregivers. Integrating strength-based approaches in clinical and educational planning may support engagement and enhance developmental outcomes. Our findings underscore the importance of holistic assessment, including both challenges and assets, in neurodevelopmental profiles.

Keywords: Williams syndrome, adaptive functioning, behaviour problems, CBCL, family perception, strengths-based assessment

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POSTER 2: Ethical Case Report: Kidney Replacement Therapy in a 15-year-old Boy with Multiple Disabilities and ADPKD: The Ethical Dilemma Between High Medical-Technical Possibilities and the Perspective of the Family and Rehabilitation Paediatrician

Presenting Author: Katleen Ballon

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Background: X is a 15-year-old boy with profound intellectual disability, epilepsy, cerebral palsy (GMFCS V, MACS V, EDACS V, FCFS IV, VFCS V), and tube feeding dependency. He has been followed by the multidisciplinary cerebral palsy team at University Hospitals Leuven since infancy. He lives at home with his loving family and receives home-based special needs support. At age 12, X was incidentally diagnosed with autosomal dominant polycystic kidney disease (ADPKD). His father and eldest sister are also carriers of this condition; other siblings have not yet been screened. Renal function declined rapidly, prompting consideration of kidney replacement therapy (KRT). Despite his complex condition, X enjoyed a good quality of life. His parents wished to pursue treatment. Given the familial nature of ADPKD, the potential for living-related kidney transplantation (KT) added further complexity to the ethical discussion.

Methods: A multidisciplinary meeting was held, involving the nephrology team, transplant surgeon, and rehabilitation paediatrician. The limited available literature on KRT in children with severe disabilities was reviewed to guide discussion. Treatment options and their implications were discussed in detail with the family, focusing on quality of life.

Results: While the nephrology and transplant teams initially preferred KT, the cerebral palsy team—represented by the rehabilitation paediatrician—advocated for a less invasive approach and even raised the possibility of palliative care. Ultimately, consensus was reached to begin nocturnal peritoneal dialysis.

Conclusion: Initiating KRT in children with severe developmental disabilities remains ethically complex and delicate. This case illustrates how multidisciplinary collaboration—balancing medical-technical possibilities with broader quality-of-life considerations and family values—can guide ethically sound decision-making.

Keywords: Ethics, personalised care, helicopter view, multidisciplinary

POSTER 3: Nurturing Brain Plasticity: Impact of Environmental Enrichment for Children with Developmental Disabilities and Behavioural Phenotypes: Bridge from Theory into Practice... Yes we Can!

Presenting Author: Katleen Ballon

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Background: Having the experience of working in the daily reality at the Center for Developmental Disorders at the University Hospitals Leuven and being aware of the concept of brain plasticity and effects of environmental enrichment, the idea grew of an innovative and inclusive childcare concept. The mission of family-centred inclusive nursery Villa Clementina- founded 2014 - is that childcare should be a possibility for every child regardless the

socio-economical background or medical problems. Also severely disabled and autistic children are welcome.

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

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

Conclusion: A thorough inclusive childcare setting can provide a context for environmental enrichment in a critical window for learning and thus harness neuroplasticity and influence behavioural phenotypes.

Keywords: Brain plasticity, environmental enrichment, inclusion, Smith Magenis syndrome

POSTER 4: Neuroimaging of Cerebral Amyloid Angiopathy in Down Syndrome: A Systematic Review of Marker Prevalence, Imaging Manifestations, Age-Related Changes, and Monitoring Strategies

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Background: Individuals with Down Syndrome (DS) are significantly at risk of developing Alzheimer's Disease (AD) which is often accompanied by Cerebral Amyloid Angiopathy (CAA), a vascular disease that may influence disease progression and therapeutic outcomes for people with AD. Despite the growing understanding of the relationship between CAA and sporadic AD, the clinical and imaging manifestations of CAA in DS remain poorly understood. Neuroimaging analysis plays a crucial role in early detection, risk stratification and disease monitoring. This review aims to synthesise current evidence on the prevalence, imaging characteristics, and clinical relevance of CAA-related neuroimaging markers in people with DS.

Methods: A comprehensive search has been conducted via EMBASE, PubMed, MEDLINE and PsycINFO for observational studies on CAA in DS focusing on neuroimaging markers and age-related changes. Two reviewers will independently screen articles and extract data on study characteristics (authors, year, design, sample size), participant demographics (age, sex, cognitive status), and the presence and distribution of various neuroimaging markers of CAA such as cerebral microbleeds, white matter hyperintensities and perivascular spaces. Data on age-related progression, and any reported monitoring or follow-up strategies will also be extracted.

Results: Findings will be narratively synthesised to present the prevalence, distribution and age-related progression of neuroimaging markers and any reported association with clinical features such as cognitive decline. Preliminary data suggests potential unexplored markers of CAA such as cortical microinfarcts as well as age-dependent expression and the significance of age-related variations in CAA presentation.

Conclusion: By characterising the neuroimaging features of CAA in DS, this review will contribute to defining a CAA-AD biomarker profile specific to DS, inform the development of clinical monitoring protocols, and support the broader goal towards personalised medicine for individuals with DS. It will also identify key gaps to inform and direct future research in neuroimaging and AD care in people with DS.

Keywords: Down Syndrome, Alzheimer's Disease, Cerebral Amyloid Angiopathy, Neuroimaging

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POSTER 5: The Social Behavioural Phenotype of Children and Adolescents with Fragile X Syndrome and Autism Spectrum Disorder: The Role of Sensory Processing

Presenting Author: Nienke Bouw

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Background: Fragile X syndrome (FXS) is the most common single-gene cause of Autism Spectrum Disorder (ASD). Relevant to the social behavioural difficulties, as found in FXS, is the notion that processing of sensory information plays an important role in the emergence and continued existence of behavioural difficulties. This study firstly aims to investigate the behavioural phenotypical overlap in terms of general behavioural problems (internalizing and externalizing) between children and adolescents with FXS and children and adolescents with ASD, and more specific in social communication and interaction, and repetitive behaviour. Our second aim is to understand if and how difficulties with sensory processing may serve as transdiagnostic mechanism leading to behavioural and social difficulties.

Methods: Questionnaires were administrated to parents to investigate the social behavioural phenotype of children and adolescents with FXS: the Child Behavior Checklist (CBCL) to get insight in behaviour problems, the Social Responsiveness Scale (SRS) to measure ASD symptomatology, the Repetitive Behaviors Scale-Revised (RBS-R) to measure repetitive behaviour and interests and the Sensory Profile (SP) to investigate sensory processing. Besides the SRS, the Autism Diagnostic Observation Schedule (ADOS) was used to study ASD symptomatology. Results in the FXS group will be compared to the ASD group and a typically developing (TD) group.

Results: The results of the study are not yet known, but will be presented at the SSBP conference. We 1) hypothesize that children and adolescents with FXS show more behavioural difficulties, repetitive behaviour and interests, and vulnerabilities in social communication and interactions as compared to ASD en TD peers. Also, we hypothesize that children and adolescents with FXS and ASD show different sensory processing, as compared to the TD group. Next, we 2) hypothesize that difficulties with sensory processing serve as a mechanism underlying behavioural and social difficulties in children and adolescents with FXS.

Conclusion: Results will provide insight in transdiagnostic mechanisms, specifically sensory processing, underlying the social behavioural phenotype of FXS. This may point to markers that can be used in clinical practice to support development of children and adolescents with FXS.

Keywords: Fragile X, autism spectrum disorder, social behaviour, sensory processing

POSTER 6: The Social Behavioural and Social Cognitive Phenotype in Children and Adolescents with Fragile X Syndrome and Autism Spectrum Disorder

Presenting Author: Nienke Bouw

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Background: About ~1 in 4,000 boys and 1 in 8,000 girls are born with Fragile X Syndrome (FXS), caused by an expansion of a CGG repeat of the FMR1 gene on the X chromosome. The majority of individuals with FXS show symptoms of autism spectrum disorder (ASD). This cross-sectional study was designed to investigate the phenotypical overlap and differences in social behaviour and social cognition in children and adolescents with FXS and an age-matched heterogeneous ASD sample, compared to a typically developing control sample.

Methods: Participants in the current study were 14 children with FXS, 24 children with ASD and 19 typically developing controls, aged 6-18 years. Social behaviour was assessed, using parent report (CBCL, SRS) and structured behavioural observations (ADOS). Next to this, basic visual social attention towards faces and autonomic arousal were measured during an emotional oddball paradigm, and Theory of Mind (ToM) abilities were investigated with the ToM task of the NEPSY-II-NL.

Results: Results showed more social difficulties in the FXS and ASD group, as compared to the typically developing group. Next, disturbances in social cognition in FXS were found, compared to the ASD and typical developing control group, in terms of decreased visual attention to social information. Regarding implicit emotion recognition, the attentional difference between the FXS group and the TD group was surprisingly smaller after conflicting multisensory emotional information. However, a lack of arousal response to conflicting emotional information was found in the FXS group. Also, in FXS, difficulties with ToM were found.

Conclusion: Given the significant impact of social cognition on adaptive day-to-day social functioning, deviations in basic and more complex social cognitive abilities could be an important underlying mechanism in explaining the social difficulties and related risk on a clinical diagnosis of ASD described in individuals with FXS.

Keywords: Fragile X syndrome, autism spectrum disorder, social cognition, social attention, autonomic arousal, theory of mind

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POSTER 7: Longitudinal Changes in Challenging Behaviour and Autistic Symptoms in Individuals with Smith-Magenis Syndrome

Presenting Author: Monica Stolen Dønnum

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Background: The prevalence of challenging behaviour in individuals with Smith-Magenis syndrome (SMS) is notably high, yet its longitudinal development remains underexplored. This study investigates the trajectory of challenging behaviour and autistic symptoms in 16 individuals with SMS over a seven-year period.

Method: Challenging behaviour and autistic symptoms were assessed at two time points approximately seven years apart, using the Developmental Behaviour Checklist (DBC), the Social Communication Questionnaire (SCQ), and the Social Responsiveness Scale (SRS). We compared scores from the two assessments using t-tests. Additionally, we explored potential correlations between score changes and participants' age, sex, Vineland and DBC scores at baseline, and SCQ scores above and below the cut-off, utilising Pearson's correlation and t-tests.

Results: The mean SCQ scores were at the cutoff of ≥ 15 , with 9 of 16 participants scoring above this threshold, indicating a high prevalence of autism. Mean SRS scores exceeded 60, suggesting significant social impairment, and all DBC scores were above the threshold of 46, indicating severe behavioural disturbance. SRS scores showed a significant reduction from T1 to T2 ($p < 0.001$), as did DBC scores ($p = 0.02$). No significant change was observed in SCQ scores. We found no significant correlations between score changes and variables such as sex or SCQ-based autism grouping.

Conclusions: This longitudinal study confirms persistently high levels of challenging behaviour in individuals with SMS. Despite this, we observed a significant reduction in both social impairment and behavioural disturbance over the seven-year period. The underlying causes of this improvement remain unclear, and no specific factors were identified as influencing the degree of change.

Keywords: Smith-Magenis syndrome, Challenging behaviour, Autism spectrum symptoms; Longitudinal study, Behavioural assessment, Developmental disabilities

POSTER 8: Psychiatric Symptoms in Smith-Magenis and Potocki-Lupski Syndromes: Preliminary Findings from a Norwegian Cohort

Presenting Author: Monica Stolen Dønnum

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Background: Smith-Magenis syndrome (SMS) and Potocki-Lupski syndrome (PTLS) are rare genetic neurodevelopmental disorders caused by a deletion (SMS) or duplication (PTLS) of chromosome 17p11.2. SMS may also result from mutations in the RAI1 gene. Intellectual disability (ID) and autistic traits are common in both syndromes. Although psychiatric comorbidity is frequent in individuals with ID and autism, little is known about the prevalence of psychiatric disorders in SMS and PTLS.

Method: We assessed psychiatric symptoms in 10 individuals with SMS and 9 with PTLS, aged 2–68 years (5 under age 12), using the Psychopathology in Autism Checklist (PAC). The participants were recruited from Frambu Resource Center for Rare Disorders, and the outpatient clinic for habilitation services for adults. The PAC includes 42 items across five subscales: psychosis, depression, anxiety, obsessive-compulsive disorder, and general adjustment problems. Each subscale has a clinical cut-off. Results are reported as group medians to protect participant confidentiality.

Results: In the SMS group, median scores for general adjustment problems and depression exceeded clinical cut-offs. In the PTLS group, all median scores were below cut-offs. Five PTLS participants had no subscale scores above cut-off, compared to only two in the SMS group. Three PTLS and two SMS participants scored above cut-off on general adjustment problems and one additional subscale. One PTLS and six SMS participants exceeded cut-offs on general adjustment problems and at least two other subscales.

Conclusions: Psychiatric symptoms appear common in both SMS and PTLS, particularly in SMS. Based on PAC guidelines, 4 of 9 PTLS and 8 of 10 SMS participants should be referred for further psychiatric evaluation. These findings underscore the need for increased clinical awareness and further research into psychiatric comorbidity in these rare syndromes.

Keywords: Smith-Magenis syndrome, Potocki-Lupski syndrome, Psychiatric symptoms, Intellectual disability, Autism spectrum, Psychopathology

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POSTER 9: Characterising Anxiety and Emotional Outbursts: Insights from Families of People with Rubinstein-Taybi Syndrome

Presenting Author: Courtney Greenhill

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Background: Anxiety and emotional outbursts are prevalent concerns in individuals with rare genetic syndromes associated with intellectual disability. Emerging evidence supports syndrome-specific conceptualisations of emotional difficulties to improve targeted intervention. Rubinstein-Taybi Syndrome (RTS) is associated with elevated anxiety and emotional outbursts; however, detailed phenotypic descriptions remain limited. This study provides the first bottom-up exploration of anxiety and emotional outbursts in RTS using clinical interview methodology.

Methods: Twenty-three parents/carers of individuals with RTS (mean age: 15.28, SD = 10.91, range 6-49, 16 females) completed an adapted semi-structured clinical interview. Topics included onset, situational triggers, behavioural manifestations and age-related patterns. Responses were coded and analysed quantitatively.

Results: Eighteen parents/carers (78.3%) reported anxiety to impact their child, with 43.5% indicating moderate to severe impact. Among those who reported frequency, 61.5% observed anxiety daily or every few days. Sensory sensitivities (n=11) were the most frequently reported trigger, while increased motor activity (n=9) was the most observed anxiety-related behaviour. Emotional outbursts were reported by 22 parent/carers (95.7%), with daily angry emotions (n=8) and outbursts exceeding five minutes (n=10). Common antecedents included restriction or denied access (n=16), such as being told “no”, having an item removed, or being instructed to do something.

Conclusions: Anxiety and emotional outbursts are highly prevalent and impactful in RTS. Findings highlight the need for syndrome sensitive assessment and support strategies. The identification of transdiagnostic constructs, such as sensory sensitivity, intolerance of uncertainty, and emotional dysregulation, may guide the development of personalised interventions.

Keywords: Rubinstein-Taybi Syndrome, intellectual disability, anxiety, emotional outbursts

POSTER 10: Ethical challenges in the Treatment and Care Process for TSC-Associated Neuropsychiatric Disorders (TAND) - A Study Protocol

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Background: Tuberous Sclerosis Complex (TSC) is a rare genetic disorder in which 90% of individuals experience TSC-Associated Neuropsychiatric Disorders (TAND). These are often under-recognised and insufficiently addressed. As with other rare diseases (RD) with behavioural and neuropsychiatric disorders, TAND presents complex, lifelong challenges that extend beyond medical treatment and affect daily life. Research on chronic neuropsychiatric disorders highlights ethical challenges in care relationships, both in formal healthcare and informal settings. These include issues such as limited access to treatment, respect for autonomy, decision-making tensions, relational responsibilities, and caregiver burden. However, research on RD has primarily focused on ethical challenges related to genetic testing, clinical trials, and access to orphan drugs, while leaving the ethics of care relationships underexplored. This study, framed within the TANDem-2 project, seeks to address this gap by examining the ethical dimensions of care experiences in TAND. It aims to: (1) identify ethical considerations in existing qualitative research on TSC care; (2) explore how individuals with TAND, caregivers, and healthcare providers experience and navigate ethical tensions; and (3) develop evidence-based recommendations for holistic TAND Care.

Methods: For Aim 1, a scoping review of qualitative literature will be thematically analysed to identify ethical issues in TSC care. For Aim 2, semi-structured interviews with key stakeholders in two locations, Chile and the United Kingdom, will be analysed using Interpretative Phenomenological Analysis. For Aim 3, a Delphi process with the TAND Consortium, analysed via Grounded Theory, will inform ethical recommendations.

Results and Conclusions: This original qualitative study, informed by an 'Ethics of Care' framework, will generate recommendations for person-centred care in TAND based on lived experiences and relational dynamics of care. Moreover, the study will provide a transferable ethical framework to guide professionals, support families, inform training, and improve care practices in TSC and other RD with complex neuropsychiatric profiles.

Keywords: Tuberous Sclerosis Complex, TSC-Associated Neuropsychiatric Disorders; TAND, TANDem, Care Ethics, Person-Centred Care

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POSTER 11: Feedback Learning and Pupil Dilation in Intellectual Disability: Insights from Williams and Fragile X Syndromes

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Background: Intellectual disability (ID) is associated with diverse cognitive and physiological profiles, yet the mechanisms underlying feedback learning remain poorly understood. Williams syndrome (WS) and Fragile X syndrome (FXS) are genetic conditions commonly associated with ID, with alterations in attention, executive function, and arousal regulation. Although reinforcement learning paradigms offer insight into learning mechanisms, few studies have explored how individuals with WS and FXS process feedback at both behavioural and physiological levels.

Method: We investigated behavioural and physiological responses to a reward contingency reversal task in individuals with WS (n = 20), FXS (n = 12), and typically developing (TD) individuals (n = 57). Eye-tracking measures of pupil dilation and gaze behaviour were analysed for WS and TD participants. Bayesian mixed-effects models were used to examine feedback learning, pupil response, and gaze allocation across groups.

Results: All groups demonstrated expected behavioural feedback learning, characterized by switching responses after losses and maintaining choices after wins. Participants with FXS showed greater volatility by switching more after wins compared to WS and TD. In the physiological analyses, TD individuals exhibited larger pupil dilation to losses than wins, while WS individuals showed no such differentiation, suggesting attenuated physiological sensitivity to feedback valence. Additionally, WS individuals were more likely to fixate on previously non-rewarded options and spent more time fixating on the screen centre, potentially reflecting altered attentional allocation.

Conclusions: Despite comparable behavioural performance between WS and TD, WS individuals displayed reduced pupil reactivity and distinct gaze patterns in response to feedback, pointing to divergent underlying mechanisms. These findings suggest that individuals with WS may achieve similar behavioural outcomes through different cognitive or physiological processes. This study demonstrates the feasibility and value of combining behavioural tasks with physiological measures to investigate learning mechanisms in populations with genetic syndromes and ID.

Keywords: Decision-making, feedback learning, eye tracking, Williams syndrome, intellectual disability, pupil dilation

POSTER 12: Electroretinography as a Candidate Biomarker in Neurodevelopmental FMR1 Disorders

Presenting Author: Hasan Hasan

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Background: Electroretinography (ERG) is a non-invasive tool that captures retinal neurophysiological function and has gained attention for its potential as a translational biomarker in neurodevelopmental disorders. Prior studies have shown ERG abnormalities in FXS (reduced b-wave amplitude), ADHD, and ASD. Given the shared embryologic origin of the retina and brain, ERG may provide insight into CNS dysfunction across FMR1-associated conditions. This study evaluates ERG profiles in premutation carriers, FX males, FX females, and controls.

Methods: In this cross-sectional study, ERG responses were recorded under light-adapted conditions using the RETeval® handheld device (LKC Technologies, Gaithersburg, MD, USA) across three stimulus protocols. Participants included individuals with FXS, premutation, and neurotypical controls. Peripheral blood FMRP levels were quantified using a time-resolved fluorescence resonance energy transfer (TR-FRET) assay. Cognitive and behavioural evaluations included the Aberrant Behavior Checklist - Fragile X version (ABC FX), the Swanson, Nolan and Pelham Questionnaire - Fourth Edition (SNAP-IV), and the Sensory Experiences Questionnaire (SEQ). Group comparisons and correlation analyses were performed.

Results: Significant group-level differences were found in 2 Hz b-wave amplitude ($p = 0.0081$), 2 Hz b-wave time to peak ($p = 0.0164$), 28.3 Hz flash amplitude ($p = 0.0139$), 3.4 Hz red/blue b-wave amplitude ($p = 0.0026$), and PhNR amplitude ($p = 0.0026$). ERG measures showed strong intra-session reliability ($ICC = 0.71-0.92$) and high inter-protocol correlation (e.g., 2 Hz and 3.4 Hz b-wave: $p = 0.78$, $p < 0.0001$). ERG metrics did not correlate with FMRP or behavioural scores. FMRP levels, however, correlated with IQ ($p = 0.69$, $p < 0.0001$) and inversely with ABC FX, SNAP-IV, and SEQ scores.

Conclusion: ERG reveals functional retinal differences in FMR1-related groups and holds promise as a physiological biomarker. Multimodal biomarker strategies are needed to better characterize fragile X-associated conditions.

Keywords: Electroretinography (ERG), Fragile X syndrome, Biomarkers, FMR1 premutation, FMRP

POSTER 13: A Broad Exploration of Clinical Challenges in Individuals with Phelan McDermid Syndrome in Norway

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Background: Phelan McDermid Syndrome (PHMDS) is a rare genetic disorder and represents a compound phenotype that may include a range of somatic, behavioural and psychiatric challenges. However, little is known about the Norwegian population of individuals with PHMDS.

Method: All known individuals with PHMDS throughout Norway are invited to participate in this ongoing project. A broad assessment is conducted via informant interview (family member or caregiver). The interview includes standardized instruments and additional questions concerning level of functioning, language and communication, sleep, somatic illness, autism, psychiatric and behaviour problems, developmental/neuropsychiatric regression, etc.

Results: To date, 28 participants have been included in the study, representing a varied sample regarding age, and a heterogeneous phenotype regarding level of functioning, communication, autism, and behavioural and somatic co-occurring disorders. Many of the characteristics previously described in PHMDS are identified in the sample, but no characteristic appears to be present in all participants.

Conclusion: The large variation throughout the different domains assessed in the current study highlights the need for broad and individualized clinical assessments for all individuals with PHMDS. Moreover, this heterogeneity and clinical variation highlights the importance of avoiding attributions of co-occurring difficulties to PHMDS (genetic determinism), as this may lead to misinterpretation of symptoms and failure to adequately treat co-occurring difficulties. The large number of participants with severe somatic illnesses and limited spoken language skills indicate that particular attention is needed to comprehensive and regular monitoring of somatic health, preferably by experts familiar with PHMDS. Frequent reports of regression, as well as suspected mental health disorders such as bipolar disorder and catatonia, indicate that many participants need access to specialized mental health services. Furthermore, the potential need for co-occurring mental health and somatic health services highlights the need for collaboration between different parts of the health care system for these patients.

Keywords: Phelan McDermid syndrome, behavioural phenotype, psychiatric disorders, somatic illness, mental health

POSTER 14: Response Inhibition in Youth with Fragile X Syndrome

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Background: Fragile X syndrome (FXS) is caused by disruption of the fragile x messenger ribonucleoprotein 1 (FMR1) protein and is the most common single-gene cause of autism. Currently, still little is known about the neurocognitive underpinnings of the social difficulties observed in FXS. Response inhibition is important for making adequate social responses and, therefore, may be a crucial in understanding why autism is so frequently observed in FXS. In this study, we aimed to improve our knowledge of response inhibition in youth with FXS by comparing them to a group of neurotypical and a group of autistic youth.

Methods: Participants were youth with FXS (n = 29), autism (n = 29), and neurotypical youth (n = 25), aged 6-19 years. We measured response inhibition with 1) a go/no-go task and 2) the auditory attention and 3) response set tasks of the NEPSY-II-NL. The groups were compared on inhibition errors while controlling for IQ and age.

Results: The results show that youth with FXS show relative difficulties in response inhibition compared to both autistic and neurotypical youth. The FXS group made more inhibition errors on the go/no-go task, the auditory attention task, and the response set task compared to the other study groups. There were minor differences between the autism and neurotypical groups.

Conclusion: As expected, response inhibition is challenging for youth with FXS. As differences were more pronounced in when task difficulty increased, one may expect that response inhibition difficulties become problematic in FXS during situations with complex, multisensory input, such as social interactions. Future studies should focus on how social interaction in FXS is affected by the amount of sensory distraction and its relationship with response inhibition abilities.

Keywords: Fragile X syndrome, autism spectrum disorder, response inhibition, executive functioning

POSTER 15: Delineation of Cross-Domain Associations Between Everyday Executive Function and Adaptive Behaviour in Down Syndrome and Williams Syndrome

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Background: In genetic syndromes such as Down syndrome (DS) and Williams syndrome (WS), difficulties with executive functioning (EF) are a commonly reported feature using lab-based performance measures. However, it remains unknown how cross-syndrome characteristics of everyday EF relate to adaptive functioning and intelligence, and if these relationships differ across adolescence and adulthood in these genetic syndromes.

Method: This study aimed to characterise the profile of strengths and weaknesses in everyday EFs using the Behaviour Rating Inventory of Executive Function (BRIEF-A) in adolescents and young adults with DS and WS. Associations between distinct EFs, adaptive/maladaptive functioning, and intellectual ability were also investigated.

Results: We found that the WS group displayed profound impairments in almost all BRIEF-A scales, with a large percentage of scores in the clinically significant range. Further, selective EFs (Inhibit, Organisation of Materials, Task Monitor) were able to discriminate between the two genetic syndromes. In DS, the Task-Monitor and Shift scales were unique predictors of externalising and internalising behaviours, respectively.

Conclusion: These findings emphasise the importance of identifying syndrome-specific strengths and difficulties in distinct EFs, which can become the target for cognitive training interventions designed to improve everyday functions and detect imminent risk of early onset of cognitive decline.

Keywords: Executive function, adaptive behaviour, Williams syndrome, externalising behaviour, internalising behaviour

POSTER 16: The Cognitive and Psychiatric Trajectories of Children with Rare Neurodevelopmental Genetic Conditions: Longitudinal Findings from the IMAGINE-ID Study

Presenting Author: Josh Hope-Bell

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Background: There is a lack of longitudinal research on children with neurodevelopmental disorders of genetic origin. The IMAGINE-2 study aims to address this gap by characterising the developmental and psychiatric trajectories of children with rare genetic variants (Neurodevelopmental Copy number Variants; ND-CNVs).

Methods: Detailed in-person assessments of 332 children with a range of ND-CNVs have been completed at two timepoints (mean age T1= 9.5, T2= 13.2). Control siblings (without a known ND-CNV) were also assessed (N = 100, mean age T1= 10.4, T2= 13.9). Caregivers were interviewed about their child's psychiatric symptoms via the Child and Adolescent Psychiatric Assessment (CAPA). This provided both symptom counts and DSM-V diagnoses. IQ was measured in children by Weschler Abbreviated Scale of Intelligence (WASI). Linear and logistic mixed models were employed for longitudinal analyses.

Results: Children with ND-CNVs met research diagnostic criteria for a psychiatric diagnosis at a rate of 72.1% at T1 and 62.1% at T2, compared with 15.2% and 12.6% at T1 and T2 for controls. Across development, children with the ND-CNVs displayed significantly higher symptoms of ADHD ($\beta=7.42$, $p < .001$), anxiety ($\beta=3.75$, $p = .028$) and mood symptoms ($\beta=2.56$, $p = .022$), compared to control siblings. Those with ND-CNVs also had lower mean IQ score than controls ($\beta = -16.78$, $p < .001$) across development. For performance IQ the difference from controls increased over time ($\beta = -1.41$, $p < .001$) indicating a developmental lag.

Conclusions: This represents one of the largest longitudinal neuropsychiatric investigations of children with ID of genetic origin. We found this vulnerable group experienced persistent psychiatric symptoms and an increasing deficit in performance IQ relative to controls, highlighting the need for greater clinical and educational support for this population.

Keywords: Neurodevelopmental disorders, copy number variants, cognition, longitudinal research, developmental trajectories

POSTER 17: Neurobehavioral Risks and Cognitive Functioning in Children with Coffin-Siris Syndrome

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Background: Coffin-Siris Syndrome (CSS) is a rare genetic disorder characterized by developmental delays and behavioural vulnerabilities. Studying children with CSS provides a unique opportunity to identify genetic factors involved in neurocognitive development, as mutations associated with the syndrome are known to influence brain maturation and may affect information processing abilities, including executive functions. This study aims to examine the behavioural functioning of children with CSS and to explore neurocognitive processes that may contribute to their behavioural and emotional vulnerabilities.

Methods: 35 children diagnosed with CSS were assessed using performance tests and parent-report questionnaires measuring cognitive abilities, behavioural problems, and symptoms of ASD and ADHD. Four cognitive domains were investigated: general cognition, expressive language, receptive language and visuospatial functioning. The present study is part of a larger study in which we study neurocognitive markers for developmental vulnerabilities in rare genetic disorders.

Results: Children with CSS showed significant developmental delays in general cognition, expressive language, receptive language, and visuospatial functioning. Analyses indicated that older children deviated more from typical developmental trajectories, suggesting growing-into-deficit at the individual level. Behavioural and cognitive vulnerabilities, particularly thinking problems, attention difficulties, and social problems, were present in children with CSS. Moreover, ASD- and ADHD-related symptoms were reported. Notably, general cognitive functioning was not directly associated with behavioural functioning, indicating separate underlying mechanisms.

Conclusion: These findings suggest that children with CSS are at risk for vulnerabilities in language development, general cognition and daily functioning. This knowledge is important to learn more about risk factors in development, and may help direct preventive therapeutic intervention. The lack of a direct link between general cognition and behavioural functioning highlights the need for further investigation into specific neurocognitive domains, such as social cognitive functioning and self-regulation, which might predict developmental vulnerabilities in behavioural and adaptive functioning in children with CSS.

Keywords: Coffin-Siris Syndrome, cognitive functioning, language development, social cognition, behaviour

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POSTER 18: Neurodevelopmental Copy Number Variants Increase Risk of Internalising and Cardiometabolic Multimorbidity

Presenting Author: Ioanna Kyriaki Katzourou

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Background: Internalising and cardiometabolic multimorbidity (ICM-MM) represents a major clinical challenge, negatively impacting life expectancy and quality of life and resulting in considerable healthcare costs. Individuals with a copy number variant associated with increased risk of neurodevelopmental conditions (ND-CNV) are more likely to develop mental or physical ill health, however the effects on ICM-MM remain poorly understood.

Methods: We used data from UK Biobank (ND-CNV N= 7,549, 1.62%). ICM-MM was identified using electronic healthcare records. It was defined as combinations of any internalising condition (either depression, anxiety or somatoform disorder) with each of five cardiometabolic conditions (hypertension, dyslipidemia, obesity, type 2 diabetes and chronic kidney disease). We assessed the effect of ND-CNVs on the risk of developing ICM-MM. We also studied whether ICM-MM risk in those with ND-CNV differed by sex, presence of a deletion versus a duplication and we established associations of dosage-sensitive genes within ND-CNVs with ICM-MM. Finally, we explored the interaction between presence of ND-CNV and polygenic risk scores (PRSs) of internalising and cardiometabolic traits on ICM-MM risk.

Results: The presence of ND-CNV was associated with ICM-MM (OR range 1.21-1.57). Female participants with ND-CNV were more likely to have any internalising condition and T2D, and those with a deletion any internalising condition and obesity. The number of deleted haploinsufficient genes, but not duplicated triplosensitive genes, was associated with ICM-MM. No significant interactions between ND-CNVs and PRSs were found.

Conclusion: This is the first study to report that ND-CNVs increase the likelihood of ICM-MM, and we find evidence of sex differences and stronger effects for deletions. Increased clinical awareness can help ameliorate this risk.

Keywords: Copy number variants, multimorbidity

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POSTER 19: A Population-Based Study of Academic Attainment and Behavioural Difficulties in Children with Neurodevelopmental-Risk Copy Number Variants

Presenting Author: Ioanna Kyriaki Katzourou

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Background: Recurrent copy number variants (CNVs) increase the risk of neurodevelopmental conditions (ND-CNVs) and are associated with physical health disorders. Yet, the impact of ND-CNVs on the daily functioning of children in the general population remains poorly understood. It is also unclear whether children with ND-CNVs receive a genetic diagnosis or a diagnosis of neurodevelopmental conditions (NDCs), and the educational support that could enhance their future mental and physical well-being.

Methods: The Born in Bradford (BiB) cohort follows children of mixed ancestry (59% South Asian (SA) and 41% European (EU) ancestry) from relatively deprived backgrounds over time. We called 54 ND-CNVs in children in this cohort (N=8863). We used the National Pupil Database to explore school performance and special education needs (SEN) support and the Strengths and Difficulties Questionnaire to assess behavioural difficulties. Diagnosis of genetic conditions and NDCs was extracted from electronic health records.

Results: ND-CNVs were detected in 141 (2%) of children, more frequently in children of EU (2.9%) than those of SA ancestry (1.5%) with a greater burden amongst children of EU ancestry from deprived backgrounds. Children with a ND-CNV faced early challenges in communication and language, difficulties in physical development and social skills. By age 6-7, 51.4% of children with ND-CNVs failed to meet expected academic targets. Furthermore, children with ND-CNVs reported hyperactivity and conduct problems. Only 8 (5.6%) children with a ND-CNV had received a genetic diagnosis and 12 (8.5%) a NDC diagnosis. No differences were found in SEN provision between those with and without a ND-CNV.

Conclusion: In this disadvantaged cohort, we identified ethnic and socioeconomic differences in the frequency of ND-CNVs. The great majority of children with ND-CNVs had not received a genetic or NDC diagnosis, and only a few received SEN support. These findings highlight the need for enhanced school-based support and medical service delivery. Early diagnosis of ND-CNVs and timely implementation of care and support where indicated can have lifelong benefits for children's mental and physical well-being.

Keywords: Genetic variants/ neurodevelopmental-risk copy number variants (ND-CNVs), neurodevelopmental conditions, chromosomal abnormalities, special education needs (SEN) support, behavioural difficulties

POSTER 20: Exploring Values in Healthcare Decision-Making for Individuals with Rare Genetic Neurodevelopmental Disorders and Their Caregivers: A Scoping Review and Qualitative Study

Presenting Author: Mirthe Klein Haneveld

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Background: Rare genetic neurodevelopmental disorders (RGNDs) associated with intellectual disabilities (ID) often involve multi-organ comorbidity and lifelong care needs. Developing clinical practice guidelines for this population requires alignment with the values of individuals and their families or caregivers.

Methods: We conducted a scoping review and qualitative research on healthcare-related values of individuals with RGNDs and their family/caregivers. A systematic search of MEDLINE, Embase, PsycINFO, and CINAHL identified qualitative studies on healthcare involving this population, which were analysed using content analysis. Semi-structured interviews with 18 parents of individuals with 15 different (ultra)rare conditions were analysed thematically.

Results: Based on content analysis of 98 relevant articles, important values included autonomy, person-centredness, and feasibility; healthcare professional competence and connection; and accessibility, coordination and absence of stigma in healthcare. Considerations for decision-making consisted of benefits and harms both on an individual and on the family-level, uncertainty, prioritization of health issues, and identity-related concerns. Parent interviews highlighted *proportionality* (balancing potential harm versus the need to treat and feasibility) and *equality* (including inclusivity, accessibility, and continuity of care). Healthcare decision-making was described as a collaborative effort, in which *parental involvement* and *autonomy of the individual* were main themes.

Conclusion: These findings suggest that children with CSS are at risk for vulnerabilities in language development, general cognition and daily functioning. This knowledge is important to learn more about risk factors in development, and may help direct preventive therapeutic intervention. The lack of a direct link between general cognition and behavioural functioning highlights the need for further investigation into specific neurocognitive domains, such as social cognitive functioning and self-regulation, which might predict developmental vulnerabilities in behavioural and adaptive functioning in children with CSS.

Keywords: Values, perspectives, clinical practice guidelines, healthcare, family, caregivers

POSTER 21: Blood Biomarkers for Neurodegeneration and Alzheimer's Disease in Individuals with Intellectual Disabilities: A Systematic Review

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Background: Individuals with intellectual disability (ID), particularly those with Down syndrome (DS), face a significantly increased risk of developing Alzheimer's disease (AD) and related neurodegenerative disorders. This elevated risk is partly attributable to genetic factors, such as the triplication of the APP gene in DS, as well as other, less well-understood mechanisms in non-DS ID populations. Early detection of AD in individuals with ID is particularly challenging due to a combination of factors, including the level of intellectual disability, atypical symptom presentation, and frequent comorbidities. Currently, blood biomarkers for AD and neurodegeneration, such as amyloid beta (A β), tau, and neurofilament light chain (NfL), are increasingly studied and implemented in the general population. These biomarkers are particularly promising as they offer a minimally invasive, cost-effective, and objectively measurable approach to detecting neurodegenerative changes. However, their applicability in individuals with ID remains largely unclear. This systematic review aims to synthesise current evidence on blood-based biomarkers for AD and neurodegeneration in individuals with ID, including those with DS, rare genetic syndromes, and ID of other aetiologies.

Methods: A comprehensive literature search was conducted across MEDLINE, Embase and the Cochrane Library using MeSH terms and relevant keywords. A total of 2,453 records were identified, of which approximately 90 studies were included in the final review. Methodological quality will be assessed using the Newcastle-Ottawa Scale. A narrative synthesis will be used due to expected heterogeneity in study designs and outcomes.

Results and Conclusions: Results will be presented, focusing on A β 40, A β 42, pTau isoforms, tTau, NfL and GFAP levels in serum or plasma. This will yield information on the use, scope and diagnostic potential of these biomarkers to address the unmet clinical need for early and accurate detection of AD in this vulnerable population.

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

POSTER 22: Investigation of Aberrant Functional Brain Network in Boys with Fragile X Syndrome and Autism Spectrum Disorder

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Background: Autism spectrum disorder (ASD) and fragile X syndrome (FXS) are behaviourally overlapped. However, little is known about the functional patterns underlying the cognitive and behavioural characteristics. This monogenetic study aimed to identify the distinct or/and shared functional networks in young boys with FXS and idiopathic ASD.

Methods: All MRI images were obtained with resting-state fMRI while sleep on GE 3.0 T Discovery 750 system after parental consent. 86 boys (age 3-8 yos) with FXS, idiopathic ASD and typical development (TD), were included. General linear regression and Kruskal-Wallis test were used to evaluate group differences in rsFC and graph theory analysis. The selected graph theory indicators are degree centrality and the area under the curve (AUC) for graph density between 5% and 50%. We divided the 160 ROIs into 8 intrinsic functional networks. Including sensorimotor (SMN), ventral attention (VAN), visual (VN), dorsal attention (DAN), default mode (DMN), frontoparietal (FPN), subcortical (SCN) and cerebellar (CN) networks.

Results: Comparison of average FC calculated within and between brain networks showed significant inter-group differences in FC within the DMN network and across 4 networks, including DMN-CN, DMN-SMN, SMN-CN, VN-CN (Fig.1). In the DMN, the FXS group consistently showed lower degree centrality and AUC at the left posterior cingulate cortex (PCC) across different network densities. In the SMN, abnormal topological features were found in the dorsal frontal cortex (dFC) and the left postcentral gyrus (PoG). Furthermore, the AUCs of both dFC and PoG were significantly increased in the FXS group.

Conclusions: This is the first study to conduct a resting-state fMRI study of boys with FXS and idiopathic ASD, revealing common and unique features of intrinsic functional networks in these two overlapping developmental disorders, helping to identify possible biomarkers or key brain areas, providing important clues for elucidating the pathogenesis and treatment of FXS.

Keywords: Fragile X syndrome, Autism spectrum disorder, Resting-state fMRI, Intrinsic network, Cognitive impairment

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POSTER 23: A Parent and a Child Both with Autism Spectrum Disorder: Challenges for the Intervention

Presenting Author: Marta Macedoni Luksic

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Background: In rare cases where both a parent and a child share the diagnostic criteria for autism spectrum disorders (ASD), the intervention needs to be adapted. The aim of our study was to analyse what adaptations of the intervention needed to be made in such cases.

Methods: Two cases of intervention are presented. In both cases, children (ages 3 and 4) and one parent were diagnosed with ASD. The intervention, in the form of an eclectic approach, was provided by the special education teacher for 16 weeks, 2 hours per week. The first 10 hours were provided in our outpatient clinic, the second 10 hours at a child's home, and 6 hours online. A method of qualitative mixed case study was used. To assess the child's adaptive behaviour, the Vineland Adaptive Behaviour Scales (2nd edition) and VB-Mapp assessment milestones were used at the beginning and after the intervention.

Results: The adaptations of the intervention that had to be made were especially in the fields of structure and organization, communication, and self-help skills. Parents with ASD had many difficulties understanding their children's very basic needs, such as feeding and sleeping. Parents with ASD struggled significantly to generalize the learning provided by the therapists in the outpatient clinic, so it was very helpful for them to conduct part of the intervention in the natural environment at home. As a result of the intervention, children's adaptive behaviour improved in both cases.

Conclusions: During the intervention, structural learning had to be applied to both the parent as well as to the child with ASD. Also, because of the difficulties with generalization that such a parent usually has, at least part of the intervention should be provided in a natural environment at home.

Keywords: Child and parent with ASD, adaptation of intervention

POSTER 24: The Prevalence of Fragile X Syndrome in England and Estimates of Under-Diagnosis

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Background: Central to the provision of appropriate healthcare services is the accurate estimation of prevalence. Prior estimates of the prevalence in the UK are almost 30 years old, and many international estimates have used a variety of methodologies, potentially limiting their generalisability.

Methods: We used linked data from the Clinical Practice Research Datalink (CPRD) Aurum database which contains longitudinal (30+ year) data on ~38 million patients. Cases were selected if they had ≥ 1 medical code indicative of FXS. Assuming a stable incidence of FXS over time, the highest observed age- and sex-specific prevalence rates were applied to UK population data to estimate a theoretical FXS population. Age- and sex-specific mortality rates were then adjusted using an FXS-to-non-FXS hazard ratio and applied to this theoretical population.

Results: A total of 1,520 individuals with FXS were identified (1.15 per 10,000). Based on this, the estimated number of prevalent FXS cases in the UK was 7,682. Prevalence was higher in males than in females, at 1.49 versus 0.82 per 10,000, respectively. The highest prevalence for both sexes occurred in the 16–20 age group, with rates of 4.10 per 10,000 in males and 1.46 per 10,000 in females. When these prevalence rates were applied to the UK population, an estimated 18,300 individuals were projected to have FXS. After adjusting for mortality, this number decreased to 16,663; an overall prevalence of 2.76 per 10,000.

Conclusion: The overall prevalence of FXS in males and females in the UK was similar to previous estimates; however, applying the highest observed age-specific prevalence rates to the general population indicates that FXS is likely under-diagnosed leading to an underestimation of true prevalence. We propose that the prevalence of 4.1 per 10,000 observed in males aged 16–20 may more accurately reflect the underlying prevalence across all age groups.

Keywords: Fragile X Syndrome, Epidemiology, Prevalence

POSTER 25: Beyond Measurement: Evaluating the Therapeutic Role of a Tailored Assessment Protocol (FRAX-TA) in Women with the FMR1 Premutation

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Background: Therapeutic Assessment (TA) is a semi-structured, client-centred approach that uses psychological evaluation as a vehicle for therapeutic change. While TA has demonstrated benefits across diverse populations, its application to genetically at-risk groups remains underexplored. Women carrying the FMR1 premutation (PM) face increased vulnerability to mood, anxiety, and cognitive symptoms—collectively termed Fragile X associated Neuropsychiatric Disorders (FXAND)—yet tailored psychological assessments for this group are lacking. This study introduces and evaluates FRAX-TA, a TA-based protocol adapted for adult PM carriers.

Methods: Eighty-one Italian women with genetically confirmed PM (mean±SD age: 50.5±9.41) were enrolled and randomized into four groups differing in the timing of a psychoeducational assessment (PA) session conducted by a cognitive behavioural therapist. All participants completed cognitive screening, biweekly psychological assessments using the Cognitive Behavioral Assessment for Outcome Evaluation (CBA-OE), and measures of current symptoms and lifetime DSM-5 Axis I disorders during the PA. Mixed-design ANOVAs and within-subject analyses were used to assess changes across time and to examine the influence of PA timing. An anonymous feedback questionnaire evaluated the participant's experience.

Results: Participants showed significant reductions in CBA-OE depression, anxiety, and psychological distress over the course of the FRAX-TA protocol. The PA session had both immediate and delayed therapeutic effects, particularly in reducing depressive symptoms and distress. Timing influenced outcomes: mid-phase delivery was associated with more stable and integrative improvements, while earlier sessions led to faster but sometimes less sustained benefits. Qualitative feedback confirmed high participant satisfaction and perceived emotional support.

Conclusion: FRAX-TA appears to be an effective, ethically grounded, and scalable protocol for women with the PM, offering therapeutic benefit even in the absence of ongoing therapy. The findings highlight the importance of PA as a potential tool for stigma reduction, improved symptom recognition and increased likelihood of initiating subsequent intervention. Future research should include control groups, larger samples, and explore personalized timing strategies to optimize outcomes.

Keywords: FMR1 premutation; therapeutic assessment; FXAND; FXTAS; FXPAC; neurodevelopmental disorders

POSTER 26: Psychiatric Symptoms in Prader-Willis Syndrome

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Background: Prader-Willis syndrome (PWS) is a multisystemic complex genetic disorder caused by lack of expression of genes on the paternally inherited chromosome 15q11.2-q13 region. Short stature, developmental delay, cognitive disability and excessive weight gain is characteristic for the disorder. Behavioral problems are common, including food seeking behavior, lack of flexibility, oppositional behaviors, interpersonal problems and abnormal emotional regulation. In PWS the prevalence of comorbid psychiatric disorders is high, including attention deficit hyperactivity disorder. The role of autistic symptoms and comorbid psychiatric disorders in the challenging behavior phenotypes associated with these syndromes is not yet fully understood. Although we have a great deal of knowledge about food seeking behavior in PWS, more knowledge is needed about other challenging behaviors associated with the syndrome. A better understanding of the relationship between ASD symptoms, psychiatric symptoms and challenging behavior in PWS can potentially lead to more accurate interventions.

Methods: Emotional and behavioral symptoms were assessed using the Developmental Behaviour Checklist (DBC). The level of psychiatric symptoms was assessed by using Psychopathology in Autism Checklist (PAC), a screening checklist designed to identify individuals with ID and autism spectrum disorder in need of psychiatric services. The PAC consist of 42 items distributed across 5 subscales, which are psychosis, depression, anxiety disorders, obsessive-compulsive disorder and general adjustment problems. All the subscales have a cut-off score.

Results: The collected data will be presented at the conference. We will present both median scores on general adjustment problem score and subscales, and how many of the participants that scores above the cut-off on both the general adjustment problem score and subscales. Relations between ASD symptomatology and other emotional and behavioral symptoms will be shown.

Conclusion: The overall prevalence of FXS in males and females in the UK was similar to previous estimates; however, applying the highest observed age-specific prevalence rates to the general population indicates that FXS is likely under-diagnosed leading to an underestimation of true prevalence. We propose that the prevalence of 4.1 per 10,000 observed in males aged 16–20 may more accurately reflect the underlying prevalence across all age groups.

Keywords: Prader-Willis syndrome, psychiatry, rare disorder

POSTER 27: Neurodevelopmental Disorders in Wiedemann-Steiner Syndrome

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Background: Wiedemann-Steiner syndrome (WSS) is a rare genetic disease caused by a heterozygous pathogenic variants in the *KMT2A*-gene, located on chromosome 11q23.3. Typical symptoms are developmental delay, characteristic facial features, short stature, and intellectual disability. There is a significant clinical variation within the group. ID is described mainly as mild and moderate, but also severe ID is reported. Neurodevelopmental disorders in WSS has been scarcely described.

Method: This study included parents of 15 children, adolescents, and adults with WSS. We used standardized questionnaires such as Social Communication Questionnaire, Sensory Responsiveness Scale, Developmental Behavior Checklist (parent) and Vineland Adaptive Behavior Scales II as measures.

Results: Eighty-six percent scored in either mild, moderate, or severe deficits on the SRS, indicating high levels of autism spectrum symptoms. Thirty-eight percent scores above the cut off on SCQ. Eighty-seven percent scores within moderately low or low adaptive behaviour on VABS II. On DBC especially, the anxiety subscale had a heightened score. The DBC also have scales connected to DSM-V disorders, and on the Anxious Behaviour Rating Scale the mean was 6.93 (highest possible score on this scale is 14). Four (27%) had a score of or above 10.

Conclusion: Persons with WSS seems to have significant issues within neurodevelopmental disorders. They also seem to have more issues with anxiety than previously reported.

Keywords: Wiedemann-Steiner syndrome, rare disorders, neurodevelopmental disorders, anxiety

POSTER 28: Awareness and Knowledge of Pediatricians Managing Developmental Delay and Intellectual Disability in Japan Regarding Genetic Testing for Fragile X Syndrome: A National Survey

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Background: Fragile X syndrome (FXS) is a common genetic condition that leads to developmental delay, intellectual disability, and autism spectrum disorder. Although genetic testing for FXS has been covered under Japan's national health insurance since 2016, the number of individuals diagnosed remains relatively low compared to other countries where testing is similarly available. This study aimed to assess the level of awareness and understanding of FXS among paediatricians who manage patients with developmental delay / intellectual disability in Japan, with a particular focus on differences between those with and without clinical genetics certification.

Methods: A nationwide survey was distributed to 1,217 certified paediatric neurologists affiliated with the Japanese Society of Pediatric Neurology and 367 members of the Japanese Society of Pediatric Genetics. An additional sample was obtained from an online mailing list of 1,469 Japanese paediatric neurologists. The questionnaire included items on demographics, knowledge of FXS, and practices related to genetic testing. Data were analysed using Chi-square and Fisher's exact tests, with statistical significance set at $p < 0.05$.

Results: Among 386 respondents, 326 had experience ordering some kind of genetic testing, including 78 certified clinical geneticists. Significant differences in knowledge were observed between clinical geneticists and non-genetic specialists. Approximately 20% of non-genetic specialists were unaware that genetic testing for FXS is covered by insurance, although this lack of awareness was less frequent among those with prior clinical experience with FXS. Across all groups, many respondents expressed uncertainty regarding the indications for ordering FXS genetic testing. Additionally, non-genetic specialists more frequently reported difficulties in providing genetic counselling, citing the psychological burden placed on mothers as a concern.

Conclusion: The findings underscore the need for enhanced education and training on FXS for paediatricians in Japan. Bridging these knowledge gaps may help improve diagnostic rates and the overall care of individuals with FXS and their families. Future initiatives should prioritize collaboration between clinical geneticists and general paediatricians and work toward establishing robust systems to support genetic counselling.

Keywords: Fragile X syndrome, genetic counselling, genetic testing, FMR1 gene, intellectual disability

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POSTER 29: Metformin Improves Behaviour in Male with Fragile X Syndrome Causing by Rare Point Mutation in FMR1 Gene

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Background: Fragile X syndrome (FXS) is the most common inherited monogenic cause of intellectual disability and autism spectrum disorder. It is typically caused by a full mutation (≥ 200 CGG repeats) in the 5' untranslated region of the *FMR1* gene, leading to hypermethylation, gene silencing, and loss of FMRP expression. Rarely, point mutations in the promoter or coding regions can also cause FXS. We present a case of FXS caused by a point mutation in *FMR1*, with a notable clinical response to metformin, suggesting its potential as a targeted treatment in such cases.

Methods: A 17-year-old male with FXS due to a *de novo* point mutation (c.199-2A>G) in the *FMR1* was assessed before and after one-year of metformin treatment. Whole-exome sequencing and Western blot analysis were used to confirm the mutation type and evaluate FMRP expression. CGG repeat sizing and methylation analysis were performed using PCR and Southern blot. Clinical, behavioural, and cognitive assessments included the Leiter-3, Vineland Adaptive Behavior Scales–Third Edition (Vineland-3), and the Aberrant Behavior Checklist–Community, Fragile X version (ABC-C_{FX}). Ethical approval was obtained by IRB, the UC Davis MIND Institute.

Results: The patient exhibited hallmark physical and behavioural features of FXS, including developmental delays, ADHD, anxiety, and limited social interaction. Genetic analysis confirmed a *de novo* splice-site mutation (c.199-2A>G) in *FMR1*, causing exon 4 exclusion. Western blot analysis showed reduced FMRP expression compared to typically developing controls. After one year of metformin treatment, adaptive behaviour improved, particularly in daily living and communication (Vineland-3), alongside a modest increase in nonverbal IQ (Leiter-3). ABC-C_{FX} scores indicated reduced irritability and hyperactivity. No adverse effects were reported.

Conclusion: These results support metformin's potential as a targeted treatment for individuals with FXS caused by rare point mutations and highlight the need for further research in broader clinical settings.

Keywords: Fragile X syndrome, FMR1 gene, FMRP, *de novo* point mutation, metformin

POSTER 30: Tuberous Sclerosis Complex–Associated Neuropsychiatric Disorders Outcomes Following Add-on Cannabidiol Treatment: 3-Month Analysis of the Open-Label Phase 3b/4 Trial EpiCom

Presenting Author: Joanne Stevens

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Background: Limited treatment options exist for tuberous sclerosis complex (TSC)-associated neuropsychiatric disorders (TAND), which affect ≈90% of people with TSC. EpiCom (NCT05864846) is evaluating behavioural and other outcomes after add-on cannabidiol (CBD; Epidyolex®[EU]/Epidiolex® [US], 100 mg/mL oral solution) treatment in participants with TSC and epilepsy; we present prespecified 3-month analyses.

Methods: Patients with TSC and moderate/severe behavioural challenges are receiving CBD ≤25 mg/kg/day and standard of care (SOC) for 26 weeks; then continuing CBD+SOC or SOC alone for up to 52 weeks overall. Outcomes are change from baseline in most problematic behaviour (MPB) on the TAND Self-Report Quantified Checklist (TAND-SQ)/Aberrant Behavior Checklist (ABC) at Week 13, and CareGI-S/CGI-Severity (CGI-S) scales at Weeks 4 and 13.

Results: At 3 months, 24 patients had enrolled and 19 started CBD. In evaluable patients (n=17), median (range) age was 21 (5–42) years. At baseline, nine patients (47%) had seizures, with a mean (SD) of four (7) seizures per 28 days. The median (range) number of antiseizure medications at baseline was 3 (1–5). Most common concomitant medications were lamotrigine (n=6 [32%]), topiramate (n=6 [32%]), and everolimus (n=5 [26%]). Five patients completed Week 13 assessments; mean (95% CI) change from baseline in MPB numerical rating scale was –4.6 (–8.1, –1.1). Of seven TAND-SQ clusters, the greatest changes were in dysregulated behaviour and overactive/impulsive scores. In ABC, the greatest changes were in irritability and hyperactive noncompliance. Fewer caregivers and clinicians rated behavioural problems as severe/very severe on CareGI-S and CGI-S at Weeks 4 and 13 versus baseline. Adverse events (AEs) occurred in 12/19 participants (63%); most common was diarrhoea (n=8 [42%]). Four participants discontinued due to AEs.

Conclusions: Despite sample size limitations, this planned 3-month analysis reported behavioural improvements across evaluated subscales after initiating CBD. The safety profile is consistent with previous studies.

Keywords: Tuberous sclerosis complex, cannabidiol, behaviour, epilepsy, TAND

POSTER 31: The Role and Tasks of the Clinical (Educational) Psychologist at the Genetic Centers Across Belgium

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Background: The clinical practice in genetics encompasses the diagnosis, multidisciplinary care and follow-up of patients (and their relatives), as well as genetic counselling. The role of the clinical psychologist is an integral part of the genetic consultation including supporting the patients in the process of understanding (medical) information, coping with different emotions (such as anxiety and guilt) and guiding the decision-making process.

Aim and methods: In March 2023, the Working Group Psychosocial Aspects of Genetics (WG-PAG) was founded to gather the 15 psychologists working in the 8 genetics centres across Belgium. The aims of the WG-PAG are to highlight the importance of psychosocial issues in clinical genetics, optimize procedures, facilitate discussion on psychosocial/ethical issues, share scientific research and promote multidisciplinary care. In order to gain insight in the role and tasks of clinical (educational) psychologists, a survey (Qualtrics) was carried out.

Results: Response rate was 93%. All psychologists working at a genetic centre hold a master's degree: 10/14 in clinical psychology and 4/14 in clinical educational sciences and neuropsychology. 9 out of 14 followed a postgraduate training in psychotherapy or family therapy and 5 have a PhD. 10/14 are involved in all phases of genetic testing (preconception, prenatal, presymptomatic, diagnostic), mainly in the domain of oncogenetics, neurogenetics, neurodevelopmental disorders (NDD/ID) and reproductive genetics. The psychologist's tasks are varied and include psycho-education, counselling (emotional support, decision-making, etc.), ethical aspects, psychodiagnostic testing, supervision and teaching.

Conclusion: The presence and role of psychologists is well embedded in the daily operation of the genetic centres as reflected in their participation in all types of consultations and all domains of genetics. Their added value in the multidisciplinary care for patients is summarized as providing emotional and psychological support and acting as a mediator/facilitator/translator between the patient and the physician.

Keywords: Clinical genetics, psychosocial care, multidisciplinary, role of clinical psychologists, emotional support

POSTER 32: Establishing a Multidisciplinary Clinic for Children with Smith Magenis Syndrome: The Leuven Experience

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

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

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

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

Keywords: Smith Magenis syndrome, multidisciplinary clinic, comprehensive and integrated care

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POSTER 33: Quality of Life and Societal Cost in Autistic Children: An Exploratory Comparative Study Pre and Post Diagnosis

Presenting Author: Leontine ten Hoopen

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Background: Previous studies showed an impact of autism on the child's quality of life and societal costs, although little is known about changes from pre- to post-diagnosis.

Methods: Therefore, our study explored the utilization of health-related services and associated costs in a group of 36 clinically referred Dutch children with autism (aged 2–10 years), pre- and post-diagnosis. Taking a broad societal perspective, we included the child's quality of life, educational needs, and absenteeism in school and leisure activities. Furthermore, we assessed the service utilization in various categories, such as healthcare, youth care, and school guidance. The caregivers, mainly the parents, provided the information.

Results: Special needs daycare was the overall major cost driver pre- and post-diagnosis. We found a non-significant decrease in total annual costs (from €6513 to €5060). Post-diagnosis, healthcare costs were halved, changing towards less somatic and more mental healthcare. No shift to adjacent cost categories was seen. At the same time, the child's quality of life improved not significantly from 0.58 to 0.66 (EQ-5D-3L), with significantly fewer everyday activity problems. In addition, we observed a trend of less school absenteeism after the diagnosis. Regression analysis identified pre-diagnostic costs as the sole independent factor influencing post-diagnostic costs, explaining 23% of the variance.

Conclusions: Our findings suggest the importance of timely clarification of autism as a foundation for informed intervention and treatment planning. This could potentially result in improved quality of life, appropriate service allocation, and reduced societal costs.

Keywords: Autistic disorder, Child, Cost and cost analysis, Burden of illness, Diagnosis, Health services, Quality of life, Societal cost

POSTER 34: Longitudinal Investigation of Motor Coordination and Early Indicators of Increased Psychosis Risk in Young People with Copy Number Variants

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Background: Motor coordination deficits are among the earliest symptoms of psychotic disorders. A range of Copy Number Variants (CNVs), including micro-deletions and micro-duplications, are linked to both motor coordination difficulties and increased psychosis risk. Prodromal symptoms are early, subthreshold signs that precede the onset of a psychotic episode and indicate elevated risk for developing psychotic disorders. This study examined whether young people with psychosis risk CNVs (PR-CNVs) exhibited greater motor coordination difficulties and whether these difficulties were associated with increased prodromal features.

Method: A total of 538 young people with a range of PR-CNVs and 246 typically developing sibling controls were assessed across up to five time points. Motor coordination was evaluated using the Developmental Coordination Disorder Questionnaire and prodromal symptoms with the Structured Interview for Prodromal Symptoms. A subsample (n~100) took part in neuroimaging, including a magnetoencephalography (MEG) resting state recording.

Results: Results showed that 89.3% of young people with PR-CNVs had indicative Developmental Coordination Disorder (DCD) compared to 19.9% of controls ($\chi^2=362.3$, $p<.001$) measured at any timepoint. In addition, 32.5% of young people with PR-CNVs exhibited prodromal features compared to 7.44% of control siblings ($\chi^2=51.82$, $p<.001$) measured at a later time. Motor coordination difficulties were associated with prodromal symptoms in young people with a PR-CNV (OR = 1.92, CI = 1.08–3.61, $p=0.033$). Comparison of beta-frequency rhythms in the motor cortex between young people with PR-CNVs and sibling controls will be presented.

Conclusions: Motor coordination impairments are highly prevalent in young people with PR-CNVs and may be an early indicator of psychosis risk. Early detection and implementation of interventions such as occupational therapy can improve motor function with possible wider-reaching benefits. Neuroimaging results may improve our understanding of neural mechanisms underlying motor coordination difficulties and be an early indicator that may predict psychosis risk.

Keywords: Motor coordination, copy number variants, prodromal symptoms

POSTER 35: What are we Measuring? Classifying Outcome Measures Used in Clinical Trials for Conditions with ID

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Background: There has been a recent increase in clinical trials for conditions in which neurodevelopmental disorders, including intellectual disability (ID), are the focus of the target sample, with outcome measures relating to clinical manifestations of ID. While there are efforts to both personalize and systematize such trials, there has been little attention to expanding evidence of validity of outcome measures through their use across such trials.

Methods: A scoping review was conducted using a systematic search of bibliographic databases on December 19, 2024 to identify reports of completed clinical trials of medications, supplements or devices. We focused on reports from 2019 of samples including children with intellectual disability. We selected five outcome domains considered highly relevant for neurodevelopmental conditions: expressive communication, cognitive functioning, adaptive functioning, fine motor, or emotion regulation. We screened citations and full-text articles in duplicate and summarized trial outcome measures and author-labelled domains for eligible reports.

Results: From >8,000 citations retrieved by the search, 129 trials were identified assessing the five domains, with 88 unique outcome measures described as primary outcomes. 28 unique measures assessed expressive communication, 31 assessed cognitive functioning, 23 assessed adaptive functioning, 16 assessed fine motor, and 31 assessed emotion regulation. While most measures were identified by authors as capturing the domains of interest explicitly, there was significant variability in terminology used across studies, particularly in the emotional regulation domain.

Conclusions: With the large number of trials involving samples of intellectual disability published in the last five years, it is apparent that there is a need for a systematic approach to categorizing the concepts used in trial measures, especially for primary outcomes. Such systematization will help the field harmonize and collect data for measurement use, as core outcome sets and clinical outcome assessment regulatory approvals requiring well-established measures become more prevalent.

Keywords: Outcome measures, clinical trials, intellectual disability, concepts of interest

POSTER 36: Phenotypic Profiles Associated with Tubulinopathy Conditions

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Background: *Tubulins* are a family of proteins essential for cellular functioning, some of which play a major role in brain development. Small genomic changes ('missense variants') in tubulin-encoding genes result in rare neurogenetic conditions called "Tubulinopathies", which involve altered brain structures and neurodevelopmental challenges. Because of advances in genomic testing, an increasing number of children are receiving Tubulinopathy diagnoses, but little prognostic information is available for families to inform intervention and educational planning. The present study begins to address this knowledge gap by characterizing development in Tubulinopathies caused by missense variants in several tubulin genes.

Methods: Thirty-one caregivers completed the Developmental Profiles 4th Edition (DP-4) parent/caregiver checklist, reporting on their family members with TUBA1A (n = 7), TUBB2A (n = 9), TUBB2B (n = 5), and TUBB3 (n = 10) Tubulinopathies. The majority of participants were children (M = 7.76 years; SD = 5.86). Approximately 70% had co-occurring vision challenges and 63% had seizure disorders.

Results: Across the entire sample, global development delays were observed for the majority of participants on the DP-4 General Development Score (GDS; M = 58.66; SD = 14.72). TUBB3 conditions were associated with milder developmental delays overall (GDS M = 69.78; Range = 47-98). Participants with TUBA1A conditions demonstrated moderate degrees of delay (GDS M = 56.57; Range = 47-77). Participants with TUBB2A and TUBB2B conditions demonstrated the most pronounced degrees of delay (GDS M = 51.44 and 54.00, respectively; ranges 47-61 and 47-74). Developmental outcomes were more delayed in the presence of co-occurring vision and neurological conditions.

Conclusion: Participants with Tubulinopathy conditions demonstrated some shared characteristics, with overall severity of delay varying by which tubulin gene was affected. Additional investigation into developmental trajectories in this population can inform tailored and personalized interventions for individuals with rare Tubulinopathy conditions.

Keywords: Tubulinopathy conditions, rare disorders, neurodevelopment

POSTER 37: Beyond the Extra X and Y Chromosome: The Contribution of Familial Risk for Psychopathology to the Neurodevelopmental Phenotype of Children with Sex Chromosome Trisomy

Presenting Author: Sophie van Rijn

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Background: Individuals with an extra X or Y chromosome (sex chromosome trisomy or SCT) have an increased risk for symptoms of psychopathology and neurocognitive dysfunction. In this study we evaluated the contribution of family history of neuropsychiatric or neurocognitive disorders to the phenotype of SCT.

Methods: 106 children with SCT and 102 non-clinical controls, all aged 1-7 years, and their primary caregiver (parent) participated. Rates of neuropsychiatric and neurocognitive disorders were collected for all first-degree family members of the children. Neurocognitive tests and parental questionnaires were used to evaluate children's neurobehavioral and neurocognitive phenotypes.

Results: Results showed no systematic differences in family history of neuropsychiatric and neurocognitive disorders between the SCT group and control group. No significant effect of family history of psychiatric disorders was found on any of the child outcomes. Family history of neurocognitive disorders had a single significant effect on child outcomes: Inattention problems in SCT were higher with a positive family history of neurocognitive disorders, showing dosage response effects.

Conclusion: Familial factors may only minimally contribute to the overall phenotype of SCT on group level, although a positive family history of neurocognitive disorders may contribute to ADHD inattention symptoms in children with SCT, beyond risk associated with the extra X or Y chromosome.

Keywords: Sex chromosome variations, Sex chromosome aneuploidy, Klinefelter syndrome, Trisomy X, Familial risk, Behaviour, Cognition

POSTER 38: Foundations of Executive Function and Early Social Communication in 1-year-old Children with Down Syndrome

Presenting Author: Madison Walsh

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Background: Although approximately 18% of individuals with Down syndrome (DS) meet criteria for autism spectrum disorder (ASD), the emergence of DS+ASD remains poorly understood. ASD affects the development of social communication, and caregiver ratings of early regulatory function have been linked to later ratings of social communication skills in infants with DS. To further this work, this study examined whether precursors to the cognitive regulatory skills known as executive functions (EFs) are associated with social communication presentations in young children with DS.

Methods: Participants were 75 children with DS between 17 and 24 months ($M = 20.66$, $SD = 1.61$, female = 53%). Caregivers completed the Early Executive Functions Questionnaire (EEFQ) and the Communication and Symbolic Behaviour Scales Developmental Profile (CSBS-DP).

Results: Relatively higher means (connoting stronger EF) were observed for the Working Memory ($M = 4.59$, $SD = .95$) and Regulation EEFQ subscales ($M = 5.7$, $SD = .82$), and relatively lower means were observed for the Inhibitory Control ($M = 3.86$, $SD = .89$) and Flexibility ($M = 3.58$, $SD = .78$) subscales. Inhibitory control and working memory were associated with multiple aspects of social communication (inhibitory control r 's with communication [$r(73) = .46$, $p < .001$], expressive speech [$r(73) = .31$, $p = .006$], and symbolic communication [$r(73) = .51$, $p < .001$]; working memory r 's with communication [$r(73) = .30$, $p = .009$], expressive speech [$r(73) = .24$, $p = .035$], and symbolic communication [$r(73) = .51$, $p < .001$]. The EEFQ Regulation subscale, which assesses early emotion regulation, was not significantly correlated with CSBS composites.

Conclusions: Aspects of cognitive regulation, including inhibitory control, working memory, and flexibility, but not emotion regulation, were associated with ratings of social communication in 1-year-old children with DS. Future research should leverage direct assessment to further evaluate regulatory vulnerabilities and ASD outcomes in DS.

Keywords: Down syndrome, executive function, social communication profiles

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POSTER 39: Characterizing Early Social Communication Profiles in Toddlers with Sex Chromosome Trisomy

Presenting Author: Rebecca Wilson

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Background: Sex Chromosome Trisomy (SCT) conditions, including XXY, XYY, and XXX, occur in 1:500 children and are associated with increased rates of autism spectrum disorder (ASD)—estimated at 18% for XXY, 15% for XXX, and 30% for XYY. Understanding early social development in SCT is essential for identifying early ASD predictors and guiding targeted interventions.

Methods: Fifty-six children (XXY=34, XYY=4, XXX=18) with prenatally diagnosed SCT completed the Autism Diagnostic Observation Schedule-2nd Edition (ADOS-2) at 12 and 36 months as part of the eXtraordinary Babies Study. Item-level and domain summary scores were analysed across timepoints. Clinical ASD diagnoses were tracked.

Results: At 12 months, participants showed elevated ADOS-2 Toddler Module scores in early social communication (e.g., limited gestures, pointing), with minimal issues in restricted and repetitive behaviours (RRBs), distinguishing them from typical ASD profiles. By 36 months, many early communication challenges had improved; however, decreased eye contact persisted in 58% of participants. New difficulties emerged in areas such as conversation, with over 70% scoring in the impaired range. Trajectories across all social communication categories will be presented. Only 2 children (1 XXY, 1 XYY; 3.5%) had received a clinical ASD diagnosis by 36 months—lower than previous SCT estimates and comparable to general population rates.

Conclusion: Toddlers with SCT show distinct social development trajectories, with some early social delays improving by age 3, but persistent challenges such as reduced eye contact and emerging deficits in conversational skills. The lower-than-expected rate of ASD diagnosis highlights the importance of ongoing monitoring. Continued prospective follow-up will help determine whether social communication differences resolve, evolve, or lead to later ASD diagnoses.

Keywords: XXY, Klinefelter syndrome, XYY, Trisomy X, social development, autism

POSTER 40: Longitudinal Trends of Behavioural Characteristics in DDX3X Syndrome

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Background: DDX3X syndrome is a rare genetic condition characterised by varying degrees of intellectual disability (ID), developmental delay, autism, attention deficit hyperactivity disorder (ADHD) and behavioural difficulties. The natural history of these behaviours is unknown. We report longitudinal trends in mental health and behavioural characteristics of fourteen children and young women (CYW) with DDX3X syndrome.

Methods: Fourteen CYW with DDX3X variants aged 7 to 22 (100% female, mean enrolment age=13.85 years) were identified from IMAGINE-ID, a national cohort study of neuropsychiatric risk in children with genetic ID. Behavioural characteristics were assessed on enrolment and at two follow-up points over 6 years. On each occasion, behaviour was quantified using the Strengths and Difficulties Questionnaire (SDQ). The SDQ provided a total behavioural difficulty score alongside emotional, conduct, hyperactivity/inattention, and peer relationship sub-domain scores, which were compared to population based, normalised SDQ scoring criteria.

Results: SDQ total scores were moderately elevated (mean=14.3, $\sigma=6$) throughout childhood and adolescence, with no differences observed across different age groups ($F(1.89,9.46)=0.52$, $p=0.59$). Compared to population norms, hyperactivity/inattention and peer relationship difficulties were heightened in DDX3X syndrome, whilst conduct and emotional difficulties were less pronounced. There was a trend for hyperactivity/inattention ($r=-0.36$, $p=0.09$) and conduct difficulties ($r=-0.41$, $p=0.05$) to affect younger children (5-15 years) and improve in later adolescence (>16 years). Peer and emotional difficulties persisted into early adulthood.

Conclusions: Significant behavioural difficulties can manifest throughout childhood and adolescence in DDX3X syndrome. At a younger age, these are characterised by hyperactivity/inattention, which improve over time, whilst peer relationship difficulties may persist into early adulthood. Larger longitudinal studies are needed to confirm the observed behavioural trajectories.

Keywords: DDX3X, Intellectual disability, Behaviour, Autism, ADHD

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POSTER 41: Examining Prosocial Development in Intellectual Disabled Children with and without Autism

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Background: Prosocial behaviour, such as helping others, sharing and showing empathy, is an important part of social development. Less is known about how prosocial skills develop in children with autism spectrum disorder (ASD) and a co-occurring intellectual disability (ID). This study aimed to compare the development of prosocial ability in two groups of intellectually disabled children, with and without autism.

Methods: The study sample was selected from participants in the IMAGINE ID programme of research (2015-2025). Children with ID of genetic aetiology were recruited from UK NHS Regional Genetic Centres (T1) and followed up 5 years after their initial assessment (T2) with the Strengths and Difficulties Questionnaires (SDQ). Prosocial behaviour was measured by the parent-rated SDQ prosocial subscale. A prosocial change score (T2-T1) was characterised as negative “declined”, unchanged “stayed stable” or positive “improved”.

Results: Data were available on 1065 participants (median age 9 years at T1). 371 (35%) met criteria for an ASD. At T1, the ASD group prosocial scores were significantly lower than those in the non-ASD group ($p = <.001$); between T1 and T2, 47.4% improved, 22.1% stayed stable and 30.5% declined. In the non-ASD group, 39.2% improved, 24.6% stayed stable and 36.2% declined. Proportionately more children with ASD were reported to have improved prosocial behaviour over time ($p = .032$), but after adjusting for baseline prosocial scores at T1 using an ANCOVA, the significance of that change was lost ($p = .28$).

Conclusions: Initial differences between the groups in prosocial improvement from T1 to T2 may be explained by children in the ASD group starting with lower prosocial scores than the non-ASD group. Generally, children in both groups followed a similar prosocial trajectory, and ASD was not a predictor of prosocial improvement or decline in this sample. Further analyses are needed to identify factors that influence these processes.

Keywords: Prosocial Behaviour, Autism Spectrum Disorder, Intellectual Disability, Social Development

POSTER 42: Behavioural Traits Assessment for Persons with Fragile X Syndrome in Japan

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Background: In Japan, there is no system in place to assess behavioral traits, such as autism spectrum disorder (ASD) trait and adaptive behavior levels, in clinical research on fragile X syndrome (FXS). One of the reasons for this is that there is almost no contact between medical doctors who examine FXS and psychologists who assess behavioral traits. This affects not only clinical research on FXS but also daily medical practice. In this study, we aim to establish a system in which psychologists assess behavioral traits in the treatment of FXS by using online system or/and matching psychologists in Japan, and to collect behavioral traits data on FXS patients.

Methods: Tottori University in Japan, which has managed a registry for clinical trials of FXS, was the base of operations, and they asked the physicians of registered patients to cooperate in this study. After the physicians and patients gave consent to cooperate in the study, the following data were obtained by e-mail and online. For intelligence (or development) assessments, a matching system was conducted as needed. Age, gender, medical history, genetic test results, family history, ADI-R, Vineland II, intelligence (or developmental) assessment.

Results: Data from 5 patients (3 families) was collected 5 months after the start of the study. In the 2 sibling families, the older brother's receptive language adaptation level was higher than that of the younger brother in both families. Except for one mosaic case, the Vineland II adaptive behavior total score was in the 20s.

Conclusions: It is necessary to increase the number of cases and prepare for intervention studies in the future.

Keywords: Fragile X Syndrome (FXS), ADI-R, Vineland II, psychological assessment, online

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Angelman Syndrome

Alternative names

Although the term 'happy puppet syndrome', proposed by Bower and Jeavons in 1967 was widely used until the early 1990's, the eponym 'Angelman' syndrome is generally preferred by families and professionals.

First description

In 1965, Doctor Harry Angelman, a general paediatrician in Warrington, described three children with severe developmental delay, ataxia, prolonged bouts of laughter, seizures and similar craniofacial features. He referred to these patients as 'puppet children'.

Genetic aspects

Angelman syndrome is caused by a disruption of the maternally inherited proportion of chromosome 15q11.2-13 (Clayton-Smith & Laan, 2003; Knoll *et al.*, 1989) via four known genetic mechanisms (Jiang *et al.*, 1998). Approximately 70-75% of cases are caused by a de novo deletion (Knoll *et al.*, 1989; Duis *et al.*, 2022). The deletion can be further categorised as a 'Class I' or 'Class II' depending on the amount of information missing (Sahoo *et al.*, 2006), with Class I deletions representing a larger deletion, encompassing Class II. The majority of deletions in Angelman syndrome are Class II, with an estimated prevalence of between 55 and 60% of de novo deletions (Christian *et al.*, 1995). Around 2-7% of cases are caused by uniparental disomy (UPD; Duis *et al.*, 2022; Engel, 1993; Prasad & Wagstaff, 1997), where two copies of the paternal chromosome are inherited, 10-25% of cases are caused by a mutation in the UBE3A gene (Duis *et al.*, 2022; Ma *et al.*, 2023) and 2-7% of cases are caused by an imprinting centre defect (ICD; Bürger *et al.*, 1997; Duis *et al.*, 2022). In around 40-50% of ICD cases caused by an epimutation, mosaicism is identified (Buiting, 2010; see Le Fevre *et al.*, 2017 for case reports). Between 5-20% (dependent upon sample and extent of molecular investigations) of individuals with the physical and behavioural features of Angelman syndrome show no identifiable abnormalities in the 15q 11-13 region

(Clayton-Smith & Laan, 2003; Williams, Lossie, & Driscoll, 2001). Explanations for when no abnormality can be detected can be that there are currently unidentified mechanisms that affect the expression of UBE3A or there is a misdiagnosis of another syndrome that is phenotypically similar to Angelman syndrome (Bird, 2014). There are several syndromes that phenotypically overlap with Angelman syndrome which can result in misdiagnosis (for reviews of 'Angelman-like' syndromes see Tan, Bird, Thibert, & Williams, 2014; Williams, Lossie, & Driscoll, 2001). The genetic association between Angelman syndrome and Prader-Willi syndrome has evoked interest in genomic imprinting (see Brown & Consedine, 2004; Haig & Wharton, 2003 for an excellent discussion).

Many of the features of the syndrome are thought to result from impaired expression of UBE3A. This gene is found throughout the brain and has a role in proteic scavenging processes. This expression is normally determined epigenetically by a methylation pattern which is specific to the maternally inherited chromosome. Abnormal imprinting in various regions of the brain and the cerebellum are probably responsible for most of the phenotype.

Incidence/prevalence

Prevalence rates vary between 1 in 10,000 and 1 in 40,000 live births (Arregui Rementería *et al.*, 2023; Buckley, Dinno, & Weber, 1998; Clayton-Smith, 1993; Petersen, Brøndum-Nielsen, Hansen, & Wulff, 1995). Reports on the male to female ratio of Angelman syndrome are inconsistent, with estimates given between 1:1 to 1:2 (Saitoh *et al.*, 1994; Smith *et al.*, 1996).

Physical phenotype

Craniofacial features include microbrachycephaly, short, hooked nose, prognathism, wide smiling mouth, widely spaced teeth and hypopigmentation (Williams *et al.*, 2006). Facial change with age, with a 'coarsening' of facial characteristics into adulthood (Sandanam *et al.*, 1997).

Clinical phenotype

Children and adults are reported to have difficulties with movement and balance (Williams *et al.*, 2006) and ataxic gait thought to be caused by cerebellar dysfunction (Chéron, Servais, Wagstaff, & Dan, 2005). Scoliosis may develop, especially in less mobile patients. Axial hypotonia is present from birth. Limb hypertonia predominating at the lower extremities appears in infancy. As individuals with Angelman syndrome get older, they tend to become less mobile, although the majority do remain independently mobile (Larson, Shinnick, Shaaya, Thiele, & Thibert, 2015; Prasad, Grocott, Parkin, Larson, & Thibert, 2018).

Early onset of seizures in Angelman syndrome (< 3 years) is reported in over 80% of individuals (Williams *et al.*, 2006) and seizures persist into adulthood (Laan, den Boer, Hennekam, Renier, & Brouwer, 1996; Larson *et al.*, 2015; Thibert *et al.*, 2009). Abnormal EEG is found in most cases of Angelman syndrome (Boyd, Harden, & Patton, 1988) regardless of the presence of seizures (Laan & Vein, 2005).

Around 45% of individuals with Angelman syndrome have sleep difficulties (Agar *et al.*, 2021). A range of sleep difficulties are reported in Angelman syndrome, the most common of which is insomnia affecting all phases of sleep (i.e. initiation, maintenance, morning awakening) (Agar *et al.*, 2021; Bruni *et al.*, 2004; Trickett, Heald, Oliver & Richards, 2018). Other difficulties reported are sleep disordered breathing (Bruni *et al.*, 2004; Miano *et al.*, 2005, Trickett *et al.*, 2018), reduced total sleep time, sleep bruxism (teeth grinding) sleep enuresis (bed wetting), sleep-related movement disorders and excessive daytime sleepiness (Agar *et al.*, 2021; Spruyt, Braam & Curfs, 2018).

Behavioural aspects

The behavioural phenotype of Angelman syndrome is characterised by heightened levels of laughing and smiling, a happy demeanour, excessive sociability, aggression, impulsivity and sleep disorders (Horsler & Oliver, 2006a). Early work suggested that frequent laughing and smiling was neurologically driven, and therefore environmental factors were not influential (Williams, Frias, & Opitz, 1982). However, careful experimental manipulation of the environment identified that both the frequency and duration of

these behaviours are related to environmental context, namely adult interaction (Horsler & Oliver, 2006b; Oliver, Demetriades, & Hall, 2002). Increased prevalence of aggression, not self-injury, is reported (Arron, Oliver, Moss, Berg, & Burbidge, 2011), with typical topographies including hair pulling and skin grabbing (Summers, Allison, Lynch, & Sandier, 1995). Although it has been suggested that social motivation underpins the heightened aggression in Angelman syndrome, this is not shown consistently in the literature (Allen *et al.*, 2010; Radstaake *et al.*, 2013; Strachan *et al.*, 2009).

Other behaviours that have been related to the behavioural phenotype of Angelman syndrome include sensory processing impairments, particularly sensory seeking behaviours, reported in 74% of individuals (Heald *et al.*, 2019; Walz & Benson, 2002), and a specific profile of repetitive and stereotyped behaviours most notably hand-flapping (Moss *et al.*, 2009; Summers *et al.*, 1995; Walz & Benson, 2002). There have also been reports of abnormal eating and feeding behaviour in around 36% of cases (Horsler & Oliver, 2006a). These behaviours consist of overeating and a narrow range of food preferences (Clarke & Marston, 2000), and when compared to other genetic syndromes, individuals with Angelman syndrome scored higher for taking and storing food, preoccupation with food, and impaired satiety, which overlaps with the profile seen in Prader-Willi syndrome (Welham *et al.*, 2015). Recent reports have indicated that anxiety may be prevalent in Angelman syndrome, with estimates between 26-92% (dependent on measures used and age of sample) (Grebe *et al.*, 2022; Keary *et al.*, 2021; Wheeler *et al.*, 2019; Prasad *et al.*, 2018). In particular, separation from a primary caregiver is reported as a frequent cause of anxiety (Keary *et al.*, 2021; Wheeler *et al.*, 2019).

Cognitive aspects

Angelman syndrome is associated with a severe to profound intellectual disability, with deficits found in all areas of adaptive behaviour and cognition (Gentile *et al.*, 2010; Peters *et al.*, 2004). Comparisons across cognitive skills suggest relative strengths in socialisation (Peters *et al.*, 2004) and deficits in learning and attention (Jiang *et al.*, 2010; Walz & Benson, 2002). Although broad communication difficulties are shown

(Clayton-Smith & Laan, 2003), Angelman syndrome is associated with a particular communication phenotype characterized by a near universal absence of speech that is dissociated from receptive and non-verbal communicative abilities (Pearson *et al.*, 2019). Some individuals with Angelman syndrome are successful at using alternative and augmentative communication (AAC) to communicate with others (Calculator, 2013a,b; Roche *et al.*, 2020).

Genotype x phenotype correlations

Genotype x phenotype correlations have been reported with agreement that a *de novo* deletion results in a more severe and 'classical' phenotype than non-deletion mechanisms (Fridman, Varela, Valente, Marques-Dias & Koiffmann, 2002; Gentile *et al.* 2010; Lossie *et al.*, 2001; Mertz *et al.*, 2014). UBE3A pathogenic variants, UPD and ICD are associated with lower severity, frequency and later onset of seizures, earlier achievement of developmental milestones and development of obesity (Fridman *et al.*, 2002; Lossie *et al.*, 2001). Non-deletion mechanisms are also related to a higher cognitive ability and receptive language skills and greater likelihood of acquiring a few spoken words (Gentile *et al.*, 2010; Lossie *et al.*, 2001; Mertz *et al.*, 2014).

Differences in the phenotype between the non-deletion aetiologies are less researched and results are inconsistent, but a larger scale study suggests that UBE3A pathogenic variants and ICD present a milder phenotype than UPD (Keute *et al.*, 2021). Comparisons across the deletion classes (Class I and Class II) highlight Class I deletions (larger amount of information missing) as being associated with lower levels of adaptive and cognitive functioning, including expressive language (Sahoo *et al.*, 2006; Varela, Kok, Otto, & Koiffmann, 2004).

Life expectancy

It is estimated that life span may be 10-15 years shorter (Williams, Driscoll, & Dagli, 2010), although this has not been examined directly.

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Updated May 2025 – Jessica Mingins & Bethan Cornick

Autism Spectrum Disorder

Classification

Although there are some slight differences between the two main diagnostic classification systems for autism (Diagnostic and Statistical Manual [DSM]-5; American Psychiatric Association, 2022; International Classification of Disorders [ICD] 11; World Health Organisation, 2019/21) both require evidence (currently or by history) of difficulties in two core domains: (i) the ability to initiate and sustain reciprocal social interaction and social communication, and (ii) a range of restricted, repetitive, and inflexible patterns of behaviour and interests. Both classifications also include hyper- or hypo-reactivity to sensory input and/or unusual interests in sensory stimuli. Diagnostic ascertainment should specify if autism is accompanied by additional intellectual or language impairments; is associated with a known medical, genetic or environmental factor, or associated with another neurodevelopmental, emotional or behavioural condition. To meet diagnostic criteria, symptoms must be sufficiently severe to cause impairment in personal, family, social, educational, occupational, or other important areas of functioning. DSM-5 also incorporates overall severity ratings ('requiring very substantial support'; 'requiring substantial support' and 'requiring support'). Symptoms must have been present in early development although they may not become apparent until social demands exceed the individual's capabilities; symptom severity may also vary according to social, educational, or other contexts. Sub-categories of autism that were previously included in DSM-IV/ICD10 (e.g. Asperger Disorder, Autistic Disorder, Pervasive Developmental Disorder NOS) are no longer specified. (See also Hirota and King, 2023 for a general review)

Associated conditions

There is a significant association between autism and a wide range of other developmental and genetic disorders including Fragile X syndrome, Tuberous Sclerosis Complex, Angelman syndrome and Neurofibromatosis Type 1 (Lubbers *et al.*, 2024; Pan *et al.*, 2021). The comorbidity between autism and ADHD,

both at a genetic and symptom level, is particularly high (Rong *et al.*, 2021; Thapar & Rutter, 2021). There are links, too, with conditions such as maternal rubella, cytomegalovirus and phenylketonuria, although the phenotype in these cases tends to be atypical. Autistic people have a significantly increased risk of physical health problems, the most common being sensory impairments, autoimmune disorders, and obesity, gastrointestinal, and sleep disorders (Rydzewska *et al.*, 2021). Rates of functional neurological disorders are high (Vickers *et al.*, 2025); the overall prevalence of epilepsy is around 12% (Liu *et al.*, 2022) with rates being highest (20%-30%) in autistic individuals with intellectual disability. Mental health problems, especially related to anxiety and depression, are also extremely common. Although estimated rates of mental health disorders vary widely from study to study, a meta-analysis, based on cases diagnosed via clinical interview, reported an overall prevalence rate of 60% (Lai *et al.*, 2019).

Genetics

Overall heritability estimates for autism vary somewhat but median rates are around 80%. Family genetic studies indicate significantly increased rates of autism in siblings (around 20%); the "Broader Autism Phenotype" (i.e. having problems related to social, language and/or cognitive functioning) is also estimated to occur in up to 20% of first-degree family members (Thapar & Rutter, 2021). However, there is wide genetic heterogeneity, with multiple modes of inheritance including high rates of de novo mutations and a wide range of possible rare and common copy number variations (e.g. submicroscopic chromosomal deletions or substitutions), (Yasuda *et al.*, 2023). Diverse clinical phenotypes and limited sample sizes add to the challenges of identifying the specific genes involved and currently only around 10% to 15% of cases of autism appear to be associated with a known, specific, genetic mutation. Moreover, as research into the genetics of autism has progressed, the shared genetic influences between autism and other conditions, especially ADHD, has become increasingly clear (Zhou *et al.*, 2023).

Environmental risk factors

Recent research has highlighted the impact of gene-environment interactions and identified a number of potential environmental risks (Williams *et al.*, 2022). These include high maternal and paternal age; maternal health factors such as obesity, diabetes, or medications taken during pregnancy (e.g. thalidomide, SSRI's and Valproate); immune system abnormalities; pre or peri- natal perturbations, and pre-natal exposure to pollutants and pesticides. There is no evidence that MMR or other vaccines are a cause of autism (Gabis *et al.*, 2022).

Prevalence

Prevalence estimates of autism vary widely across the world (from 0.02% in China to 3.66% in Sweden; Salari *et al.*, 2022) and are affected many factors including cohort size, geographic location, and diagnostic ascertainment methods. A systematic review update, based on 71 studies (Zeidan *et al.*, 2022), reported ranges from 1.09/10,000 to 436.0/10,000, with a median prevalence of 100/10,000 (i.e. 1%). The median percentage of autism cases with co-occurring intellectual disability was 33.0%. The median male-to-female ratio was 4.2, although, increasingly, research suggests that the apparent gender bias may be at least partly due to the lower sensitivity of current diagnostic criteria for identifying autism in girls and women (Lockwood *et al.*, 2021).

Physical Phenotype

There is no distinct physical phenotype although minor physical anomalies and dysmorphic features are common and there is an increased risk of chronic and acute medical problems across the life span (Liu *et al.*, 2023). Compared to the general population, autistic people are more likely to suffer from neurological abnormalities including epilepsy, macrocephaly, hydrocephalus, cerebral palsy, migraine/headache, and congenital abnormalities of the nervous system (Pan *et al.*, 2020). However, to date, imaging studies have failed to identify any neurological anomalies that are either consistently associated with, or unique to autism.

Life expectancy/natural history

An increased risk of premature mortality in autism, especially among females and individuals of lower IQ, has been highlighted in a number of systematic reviews and is associated with a range of disorders of the nervous, circulatory, respiratory and digestive systems (Forsyth *et al.*, 2023). Among autistic adults of average or above intellectual ability, suicide is a significant cause of premature mortality, particularly among females (Santomauro *et al.*, 2024). Epilepsy is one of the most common causes of early death in individuals of low IQ (Forsyth *et al.*, 2023).

Behavioural and cognitive characteristics

Difficulties in reciprocal social communication and the presence of ritualistic and stereotyped behaviours/interests are core characteristics of autism. The onset of spoken language is often delayed and around 30% of individuals are described as having “minimal” speech. Although intellectual disability was once thought to be a common feature of autism, more recent research indicates that up to 60% of autistic people are of at least average intellectual ability (Katusic *et al.*, 2021).

Outcomes and intervention

Longitudinal studies indicate that many individuals, especially those who do not have additional intellectual disabilities, show significant improvements in core autism symptoms and behavioural difficulties with age. However, prognosis is affected by many individual and environmental factors, including severity of cognitive, social and communication impairments, and the adequacy of educational, occupational and other support systems (Howlin, 2021; 2025; Lord *et al.*, 2022; Tafolla *et al.*, 2025).

Autism is a highly heterogeneous condition and interventions must be tailored to individual and family needs. For very young children, approaches with a focus on social communication are recommended. For older children, support to enhance learning and social inclusion in school is required. Many adults need assistance to develop self-help and independence skills, and to maintain good mental health. The provision of programmes to ensure access to college, employment, and independent living is also crucial.

There are no drugs that can be used to treat autism per se, but access to adequate medical care is needed to reduce the impact of co-occurring physical and mental health problems (Fuentes *et al.*, 2021; Howlin, 2025; Lord *et al.*, 2022).

Websites:

There are numerous national and international websites offering information and support for individuals, families and professionals e.g.:

- <https://www.autism.org.uk>
- <https://www.autismspeaks.org>
- <https://www.autistica.org.uk>
- <https://sparkforautism.org>

There are also many websites designed specifically for autistic people: e.g.

- <https://www.iancommunity.org>
- <https://autisticadvocacy.org>
- <https://awnnetwork.org>

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Patricia Howlin, Updated May, 2025

CHARGE Syndrome

First Description

First described as associated features independently by Hall (1979) and Hittner, Hirsch, Kreh, & Rudolph (1979). Called CHARGE in 1981 (Pagon, Graham, Zonana, & Yong).

Genetics/aetiology

In 2004 mutations in the CHD7 gene (chromodomain helicase DNA-binding protein 7), locus 8q12.1, were identified as a primary cause of CHARGE (Vissers, *et al.*). Its genomic structure spans 188 kb and encompasses 38 exons, the first of which is noncoding. The encoded CHD7 protein is 2,997 amino acids in length and contains several domains that are characteristic for its protein family, the chromodomain helicase DNA binding proteins, an ATP-dependent chromatin remodeling protein family. Subsequent research has found a mutation in this gene in 65 – 75% of cases, but in >90% of “typical” CHARGE patients based on clinical diagnosis. CHARGE continues to be a clinical diagnosis. Not every variant in CHD7 is associated with clinical features of CHARGE. Thus, Hale, *et al.*, (2016) proposed using the CHD7 mutation as one of four major criteria for clinical diagnosis.

Incidence/prevalence

While most sources estimate incidence at 1/10,000 births, a comprehensive study of individuals in the Netherlands found between 1:15,000 and 1:17,000 (Janssen *et al.*, 2012).

Physical phenotype

The acronym was suggested by Pagon and colleagues (1981) based on common features: C – coloboma of the eye (missing part of iris and/or retina); H – heart defects; A – atresia of the choanae (bony or membranous blocking of nasal passage); R – restrictions of growth and/or development; G – genitourinary anomalies; E – ear anomalies and/or deafness. While all six features may appear, there is wide variation in both occurrence and severity. This has led to a more refined diagnostic system (Blake *et al.*, 1998) with four major features

(coloboma, choanal atresia, cranial nerve dysfunction, characteristic CHARGE ear) and a number of minor anomalies. Diagnosis is based on 3 major or 2 major and 2 minor. Other diagnostic systems have since been proposed (e.g., Hale, 2016). Diagnosis is difficult because there is great variability in presence and severity of the features.

CHARGE is the most common genetic cause of congenital deafblindness. Missing or malformed semi-circular canals and otoliths is nearly universal. Swallowing difficulties are common due to cranial nerve dysfunction. Other problems include gastroesophageal reflux, airway difficulties, chronic otitis media, sinusitis, detached retina, scoliosis, chronic constipation with megacolon, and sleep disturbances.

Cranial nerve anomalies are common in CHARGE with as many as 92% having symptoms of at least one anomaly. It is speculated that in some cases all 12 cranial nerves might be affected, but the most common are I, V, VII, VIII, and IX/X. Blake (personal communication) maintains CHARGE could be called Cranial Nerve Anomalous Syndrome.

Behavioural and psychiatric characteristics

There is variability in the presence of behavioural difficulties. Behaviour has been described as very goal directed and persistent, socially interested but socially immature, demonstrating high rates of repetitive behaviour and sensation seeking, including problems with self-regulation and transitioning between activities. The behaviours have led to diagnoses of autism, attention deficit/hyperactivity disorder, obsessive-compulsive disorder, and tic disorder. It has been proposed that pain, sensory issues, and anxiety, which produce problems with self-regulation, are major sources of the behavior (Hartshorne, Stratton, Brown, Madavan-Brown, & Schmittl, 2017).

Neuropsychological characteristics

There is considerable variability, with some children very developmentally delayed, and others graduating college. Adaptive behaviour tends to be in the low normal range, with little change over four years.

Deficits in executive functions have been identified, particularly difficulties with inhibition, shifting focus, and self-monitoring, although Skei *et al.*, (2023) found a strength in working memory. Due at least in part to sensory impairments, language development and communication may be severely delayed. Cognitive assessment is difficult in this population, however Skei *et al.* (2024) found support for latent learning capacity in CHARGE regardless of degree of deafblindness.

Useful websites/associations for more information

- www.chargesyndrome.org
US CHARGE foundation
- [CHARGE Syndrome Australasia](#)
Australasian support group
- [CHARGE Syndrom e.V.](#)
German organisation
- [Online Course - CHARGE Syndrome Association of Australasia Ltd](#)
MOOC (On-line course). Understanding CHARGE Syndrome. Produced by the CHARGE Syndrome Association of Australasia.

Timothy S. Hartshorne, June 2024

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Coffin-Lowry Syndrome

The Coffin–Lowry syndrome (CLS) (MIM 303600) is a syndromic form of X-linked dominant (Nishimoto *et al.*, 2014) mental retardation characterized in male patients by psychomotor retardation, growth retardation, and various skeletal anomalies. The condition was for the first time independently described by Coffin *et al.* (1966) and Lowry *et al.* (1971) and definitively distinguished by Temtamy *et al.* (1975), who proposed the eponym appellation ‘Coffin–Lowry syndrome’. Confirmation of the suspected X-linked mode of inheritance was forthcoming with the mapping of the disease locus to Xp22.2 by Hanauer *et al.* (1988), with the subsequent isolation of the causal gene, RPS6KA3 (Trivier *et al.*, 1996).

Genetics and molecular biology

The RPS6KA3 gene encodes a growth factor regulated serine-threonine protein kinase, Rsk2 (alternate names: p90RSK2, MAPKAPK1B, ISPK-1), which acts at the distal end of the Ras- Erk1/2 signalling cascade. Mutations in the RPS6KA3 gene are extremely heterogeneous and lead to premature termination of translation and/or to loss of phosphotransferase activity of the RSK2 protein. For the vast majority of mutations so far reported, no consistent relationship has been observed between specific mutations and the severity of the disease (Delaunoy *et al.*, 2006). However, expression of some features was found to be associated with particular truncating mutations in a few patients (Nakamura *et al.*, 2005).

Incidence / Prevalence

On the basis of the experience of the researchers, a prevalence rate of 1:50 000 to 1:100 000 may be reasonable. Approximately 70–80% of probands have no family history of CLS. This high incidence of sporadic cases may be attributed to genetic selection that occurs against hemizygous males and heterozygous females who are mentally retarded. Molecular studies have further revealed that two-thirds of cases arise from new mutations (Delaunoy, 2006).

Physical features and natural history

The typical facial aspect in adult male patients includes a prominent forehead, orbital hypertelorism, downward-slanting palpebral fissures, epicanthic folds, large and prominent ears, thick everted lips, and a thick nasal septum with anteverted nares. Orodontal findings include typically a high narrow palate, a midline lingual furrow, hyponodontia, and peg-shaped incisors. Skeletal malformations appear progressively in most patients and may include delayed bone development, spinal kyphosis/scoliosis, and pectus carinatum or excavatum. The extent of kyphoscoliosis may be such that it causes severe chronic restrictive lung disease (Venter *et al.*, 2019). Radiographic changes include cranial hyperostosis, abnormal shape and end plates of the vertebral bodies, delayed bone age, metacarpal pseudoepiphyses, and tufting of the distal phalanges.

Uncommonly associated manifestations include epileptic seizures and sensorineural hearing loss, which can be profound. Stimulus-induced drop episodes, with onset typically from mid-childhood to the teens (unexpected tactile or auditory stimuli or excitement triggers a brief collapse but no loss of consciousness), and cardiac involvement, usually in the form of mitral valve dysfunction, are often present. Reduced total brain volume, with a particular effect on cerebellum and hippocampus, has been reported in some patients. Affected newborn males often show only hypotonia and hyperlaxity of joints. However, broad, tapering fingers may also be present at birth. The typical facial appearance is usually apparent only by the second year of life and shows progressive coarsening thereafter with increasing prominence of the glabella and protrusion of the lips. Retardation of growth and psychomotor development become apparent gradually in the first years of life. Other possible early signs are sensorineural hearing deficit and microcephaly. The age of walking is delayed, and difficulties in ambulating may persist with a clumsy gait.

Female heterozygotes show variable involvement that can range from short stubby digits with normal

appearance to quite marked facial dysmorphism. Ventriculomegaly has been observed in several affected males and females.

Although accurate information is not available the paucity of reports of older affected males suggests that their life expectancy is reduced in contrast to that of females who can survive well into old age. Reported causes of death in affected males include myocarditis, pneumonia and inhalation during a convulsion. Several males have succumbed to complications following general anaesthesia for correction of orthopaedic problems or dental extraction (Hanauer & Young, 2002; Hunter, 2002).

Behavioural characteristics

Cognitive deficiencies in CLS male patients are prominent, but markedly variable in severity, including between siblings. However, the vast majority of patients are severely affected, with IQ scores ranging from moderate to profound (between 15 and 60). Very mild cases of the disease have been reported, with in particular in a few families only non-syndromic mental retardation (Field *et al.*, 2006). Delay in speech acquisition is particularly common with most reported males having a very limited vocabulary. Despite the limited verbal abilities, the communication skills are good and affected individuals are usually cheerful, easy going, and friendly.

Cognitive function of female carriers may be variably affected: it can range from normal intelligence to moderate mental retardation. Frequently, they are reported to have learning difficulties at school. Obesity, depression, psychotic behavior including schizophrenia) have been described in a few female carriers. Epilepsy may occasionally develop. Stimulus-induced Drop Episodes (SIDE) may occur in response to unexpected auditory or tactile stimulus (Rojnueangnit *et al.* 2013).

Available guidelines for behavioural assessment/treatment/management

There is no specific treatment. Sensorineural hearing deficit should be addressed very early to improve the development and quality of life of the patients. Treatment for individuals with CLS who experience drop attacks includes medications such as valproate and clonazepam or selective serotonin uptake

inhibitors. If stimulus-induced drop episodes occur with great frequency, use of a wheelchair may be required to prevent falling and injury (Hunter, 2005).

Useful Websites

U.S. National Library of Medicine (NLM), Genetics Home Reference

<https://ghr.nlm.nih.gov>

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André Hanauer, June 2010

Revised Stewart Einfeld, 2015.

Revised Navid Dadlani & Stewart Einfeld, June 2019

Reviewed Stewart Einfeld, June 2023

Coffin Siris Syndrome

First description and alternative names

The Coffin Siris syndrome was first described by Coffin and Siris in 1970. The researchers described three affected girls with intellectual disability, postnatal growth retardation, lax joints, brachydactyly of the fifth digits with absent nails, dislocation of radial heads, and absence of the fifth terminal phalanges (Coffin & Siris 1970). Alternative names include "Dwarfism-Onychodysplasia", "Short Stature-Onychodysplasia", "Fifth Digit syndrome", and "Mental Retardation and Hypoplastic 5th Fingernails".

Genetics and molecular biology

Coffin-Siris syndrome is now regarded as one of the BAF-1 disorders (Mannino *et al.* 2018). It is now regarded as of equal sex distribution in 60 molecularly confirmed cases (Santen *et al.* 2014). An autosomal dominant inheritance pattern with complete penetrance is suggested (Schrier-Vergano *et al.* 2018).

Studies have examined the candidate region for Coffin Siris Syndrome. An infant with findings consistent with Coffin Siris syndrome was reported to have an apparently balanced translocation with breakpoints at 1q21.3 and 7q34 (Mcpherson *et al.* 1997). Other research suggested a candidate region for Coffin Siris at 7q32->34 (McGhee *et al.* 2000). A partial trisomy 9p gene change has also resulted in a Coffin Siris phenotype (Temtamy *et al.* 2007). Recent advances in molecular genetics such as whole-exome sequencing has seen the identification of SMARCE1 and another seven genes (SMARCB1, SMARCA4, SMARCA2, ARID1A, ARID1B, SOX11 and PHF6) as being implicated in the syndrome (Schrier-Vergano *et al.* 2018).

Incidence/prevalence

Approximately 200 cases of Coffin Siris syndrome have been reported as of 2018 (Mannino *et al.* 2018).

Physical features and natural history

Classic clinical criteria for the diagnosis of Coffin Siris syndrome include developmental delay, hirsutism, coarse facies, feeding problems, and hypoplasia or aplasia of the distal fifth digits and nails. Mannino

et al. (2018) stressed the importance of molecular testing to confirm the diagnosis, giving an example of a patient with genetically confirmed CSS who had normal 5th digit fingers and toes bilaterally. Additional characteristics of Coffin Siris syndrome include feeding or sucking difficulties, wide mouth, thick lips, hypotonia, flat nasal bridge with broad nose, sparse scalp hair, thick and laterally placed eyebrows, microcephaly, abnormal ear placement, abnormal or delayed dentition, high arched palate, delayed bone age, coxa valga, frequent otitis media, and respiratory infections (Fleck *et al.* 2001). Head circumference-for-age percentile is generally reported to be less than the 3% to 10%. There are several reports of individuals with Dandy-Walker malformations or Dandy-Walker variants. Seizures are infrequently reported.

Behavioral and psychiatric characteristics

A few individuals have been described as aggressive or self-injurious while some have been characterized as having happy personalities. Case reports suggest autistic behaviours including preoccupations and rituals may be seen in some individuals.

Neuropsychological characteristics

The level of developmental delay varies from mild to moderate; the syndrome was initially characterized with having significant developmental delays (Brautbar *et al.* 2008). Expressive speech is significantly delayed while receptive speech may be slightly less impacted. Motor skills are somewhat less delayed. Today, individuals are generally reported to attend Special Education classes with an IEP (individualized education plan).

Available guidelines for behavioral assessment/treatment/management

Frequent infections have been reported for individuals diagnosed with Coffin Siris syndrome. Respiratory infections may be related to hypotonia, poor sucking, and aspiration besides increased susceptibility. Consultation with feeding clinics, G tube placement, fundoplication, thickened infant feedings, and careful

positioning post-feeding may be helpful. Early cardiac evaluation is suggested. Indications for surgical or medical treatment of congenital heart disease are managed the same as the general population. CNS imaging and GI evaluation may be considered. Renal ultrasound evaluation is suggested to investigate for infrequently reported renal abnormalities. Hernias and tear duct occlusion are treated as medically indicated. Myringotomy and adenoidectomy when indicated may decrease recurrent otitis. Regular audiological screening for hearing loss is recommended because of frequent otitis media. Ophthalmologic evaluations are suggested because of reported vision problems. Pediatric dental evaluation is appropriate; primary teeth are potentially retained long term.

Useful Websites

- NIH, Office of Rare Diseases Research:
rarediseases.info.nih.gov/

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Judith Hiemenga, Srinivasan Sathyanarayanan & Joann Bodurtha, 2010, Revised Stewart Einfeld, 2015
Revised Navin Dadlani & Stewart Einfeld, June 2019
Revised Stewart Einfeld 2023

Cornelia de Lange Syndrome

First description and alternative names

Cornelia de Lange Syndrome is named after a Dutch paediatrician who first described the syndrome in 1933. The disorder is occasionally referred to as Brachmann de Lange Syndrome after a German doctor who is also thought to have described a patient with the syndrome in 1916.

Incidence/prevalence

CdLS has an estimated prevalence of 1 in 10,000 to 30,000 live births (Kline *et al.*, 2018), although this is thought to be an underestimate, with more mildly affected individuals increasingly being identified.

Genetics

CdLS is caused by a deletion on the *NIPBL* gene on chromosome 5 (locus 5p13) in up to 80% of cases (Gillis *et al.*, 2004; Krantz *et al.*, 2004; Miyake *et al.*, 2005; Tonkin *et al.*, 2004; Huisman *et al.*, 2013). Mosaicism for *NIPBL* mutations is identified in 23% of individuals [Huisman *et al.*, 2013]. Additional mutations in *SMC3* on chromosome 10 (Deardorff *et al.*, 2007), X linked *SMC1a* and *HDAC8* genes (Deardorff *et al.*, 2012a; Musio *et al.*, 2006) and more recently identified *RAD21*, *ANKRD11* and *BRD4* mutations (Deardorff *et al.*, 2012b; Kline *et al.*, 2018) are reported to account for a smaller proportion of cases. All genes are involved in the structure and regulation of the cohesin complex which is crucial for neural maintenance and repair (Deardorff *et al.*, 2012b; Liu & Krantz 2009). It is probable that there are further unidentified mutations relevant to the cause of CdLS.

The *NIPBL* gene is expressed in the developing skeleton and soft tissue of the limbs, hands, spinal column, face and head including the ear canal, the atrial and ventricular areas of the heart, oesophagus, trachea and lungs (Tonkin *et al.* 2004). Individuals with *NIPBL* mutations show large variability in presentation but a larger proportion of these individuals appear to be more severely affected by the syndrome with more severe intellectual disability and limb abnormalities (Gillis *et al.* 2004; Bhuiyan *et al.* 2006; Huisman *et al.*, 2017). In contrast, mutations in *SMC1a* and *SMC3* have currently been found to result in a milder presentation

of the CdLS phenotype with less severe intellectual disability and fewer physical abnormalities (Deardorff *et al.* 2007; Huisman *et al.*, 2017).

Physical features and natural history

Individuals with CdLS typically have a low birth weight, microcephaly, small stature, upper limb abnormalities (25%) and hirsutism, although those with a milder presentation seem less affected by these problems (Deardorff *et al.* 2007; Kline *et al.* 2007). Distinctive facial features, including: synophrys, long, thick eyelashes, a long and prominent philtrum, a thin upper lip; and a downturned mouth appear characteristic of most individuals with the syndrome (Kline *et al.* 2007). CdLS is associated with many health problems (for overview see Kline *et al.*, 2018). Some of the most commonly occurring problems include: gastro-intestinal disorders, hearing and eye abnormalities, seizures, cardiac and genito- urinary problems. Gastro-intestinal disorders are particularly problematic in CdLS, with up to 80% of individuals with CdLS experiencing Gastro-Esophageal Reflux Disease (GERD) (Macchini *et al.*, 2010; Mariani *et al.*, 2016).

Little is known about the life expectancy of individuals with CdLS, although recent research studies have included participants aged 40 to 50 years and above (Cochran *et al.*, 2015; Groves *et al.*, 2018; Moss *et al.*, 2009; Nelson *et al.*, 2014; Oliver *et al.*, 2011). Gastro-intestinal disorders associated with CdLS create an increased risk of early mortality due to aspiration, leading to pneumonia in some cases. Early assessment and intervention of gastro- intestinal difficulties is of utmost importance in individuals with CdLS.

Behavioural characteristics

Self-injurious behaviour is generally thought to be more common in people with CdLS than in the general intellectual disability population (Sloneem *et al.* 2009) and reported to be influenced by anxiety, sleep problems and social reinforcement for some individuals (Arron *et al.*, 2006; Huisman *et al.*, 2018; Kline *et al.*, 2018). There is a notable association between self-injurious behaviour and associated medical conditions,

particularly gastrointestinal reflux (Huisman *et al.*, 2018; Luzzani *et al.*, 2003). Self-injurious behaviour may also be more likely in those with lower levels of intellectual ability, low levels of communication, high levels of impulsivity and the NIPBL gene variant (Selicorni *et al.*, 2021).

Self-restraint behaviours are common (Hyman *et al.*, 2002) and this has led to suggestions that individuals with CdLS may be at risk for self-injurious behaviour to become difficult to regulate. The increased frequency of repetitive behaviours within the syndrome, including repetitive movements and compulsive like behaviours such as tidying up and lining up (Hyman *et al.*, 2002; Moss *et al.* 2009; Srivastava *et al.*, 2021) also indicates that individuals with CdLS may be at risk for difficulties with behaviour regulation. Repetitive behaviours in CdLS are clinically impactful, as they are associated with distress (Srivastava *et al.*, 2021).

An association between CdLS and autism characteristics has been consistently reported (Basile *et al.*, 2007; Berney *et al.*, 1999; Bhuiyan *et al.*, 2006; Moss *et al.*, 2008; Nakanishi *et al.*, 2012; Oliver *et al.*, 2011; Srivastava *et al.*, 2014). It is estimated 43% of individuals with CdLS may show autism characteristics (Richards *et al.*, 2015). This association with autism is not solely accounted for by associated intellectual disability (Moss *et al.*, 2008), although the profile of autism characteristics appears to be different to that of non-syndromic autism including greater social anxiety, fewer sensory differences and better use of eye contact and gestures (Groves *et al.*, 2021; Moss *et al.*, 2012; Moss *et al.*, 2013). Extreme shyness and social anxiety are characteristic of many individuals with CdLS and an unusually high number of individuals with CdLS are reported to show characteristics of selective mutism (Crawford *et al.*, in review; Moss *et al.*, 2016).

In addition to social anxiety, other types of anxiety have been reported in individuals with CdLS including demand related anxiety, separation anxiety, generalised anxiety and specific phobias (Crawford, Waite & Oliver, 2017; Groves *et al.*, 2022; Johnson, 2015). Low mood has also been reported in individuals with CdLS with specific difficulties for low interest and pleasure described (Groves *et al.*, 2019; Nelson *et al.*, 2014; Moss *et al.*, 2017). These difficulties may become more prominent with age, adolescence and early

adulthood may be a period of increased difficulty (Goodban, 1993; Groves *et al.*, 2019; Groves *et al.*, 2021; Nelson *et al.*, 2014; Moss *et al.*, 2017; Richards *et al.*, 2009)

Neuropsychological characteristics

Degree of intellectual disability (ID) is variable in CdLS but most individuals show a severe or profound level of disability (30.43% severe level of ID; 45.6% profound level of ID) with notably poor expressive communication, primarily evidenced by limited or absent speech (Sarimski 1997; Berney *et al.* 1999; Kline *et al.*, 2018). The degree of ID and level of communication skills seem dependent on the phenotype; those with a milder presentation generally have a less severe degree of ID and appear more likely to acquire speech (Bhuiyan *et al.* 2006; Deardorff *et al.* 2007; Huisman *et al.*, 2017).

Recent research by has demonstrated impairments in executive function including verbal fluency and cognitive functioning. Some work suggests that inhibition and working memory are relative strengths (Johnson, 2015), whereas other work suggests impairments across all areas of executive functioning including inhibition and working memory, as well as shifting, emotional control, and planning/organisation (Perry *et al.*, 2021). Research suggests that impairments in executive function are not linked to adaptive ability but are associated with increased age, indicating that impairments in executive function may worsen with age in CdLS (Perry *et al.*, 2021; Reid *et al.*, 2017).

Age related change

There is emerging evidence indicating broad age-related changes in CdLS including increased anxiety, low interest and pleasure, social withdrawal, self-injurious behaviour and verbal working memory difficulties (Berney *et al.*, 1999; Cochran *et al.*, 2015; Groves *et al.*, 2019; Kline *et al.*, 2018; Moss *et al.*, 2017; Nelson *et al.*, 2014; Oliver *et al.*, 2011; Reid *et al.*, 2017; Sarimski, 1997) alongside the early onset of physical signs of ageing (Kline *et al.*, 2007). Biological processes that occur downstream from the genetic mutations responsible for CdLS have been implicated in these reported changes with age (Gimigliano *et al.*, 2012; Kline *et al.*, 2007).

Available guidelines for behavioural assessment/treatment/management

- Kline, A., Moss, J., Selicorni, A., Bisgaard, A-M., Deardorff, M., Gillett, P, *et al.* (2019). Diagnosis and management in Cornelia de Lange Syndrome: First international consensus statement. *Nature Reviews Genetics*. 19(10), 649-666. Summary available from: <https://www.cdlsworld.org/xwiki/bin/view/cdlsPublications/consensus/>
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- Welham, A., Moss, J. and Oliver, C. (2012). Special Report: Growing up with CdLS: Changes in adolescence and young adulthood. *Special Issue Report for the Cornelia de Lange Syndrome Foundation*. March, S1-S16.

Useful websites/associations for more information

- CdLS Foundation UK and Ireland: www.cdls.org.uk
- CdLS World: www.cdlsworld.org
- FIND resources: www.findresources.co.uk
- Oliver C., Moss J., Petty J., Arron K., Sloneem J. & Hall S. (2003). *Self-injurious Behaviour in Cornelia de Lange Syndrome: A Guide for Parents and Carers*. Trident Communications Ltd.: Coventry. – Available from the CdLS Foundation UK and Ireland.
- CdLS Foundation UK and Ireland (2007). *Facing the Challenges: A Guide for Caregivers to People with the Cornelia de Lange Syndrome* – Book and DVD available from the CdLS Foundation UK and Ireland.
- Oliver, C., Moss, J., Petty, J., Tunnicliffe, P., Hastings, R., Howlin, P., Griffith, G., Bull, L., Villa, D. and Yip, M. (2009). *Understanding and Changing Challenging Behaviour in Cornelia de Lange Syndrome*. Aerocomm Ltd: Essex -Available from the CdLS Foundation UK and Ireland.

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J Moss & C Oliver, July 2010.

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Updated: J. Mingins, J. Moss & J. Waite, July 2023

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ABSTRACTS

SYNDROMES

Cri du Chat Syndrome

First description and alternative names

First described by Lejeune in 1963, Cri du Chat Syndrome (CdCS), which takes its name from the 'cat-like cry', is often referred to as Deletion 5p- syndrome and chromosome five short arm deletion.

Incidence/prevalence

The prevalence of CdCS has been estimated at 1 in 50,000 live births and although the exact gender ratio is unknown, the syndrome is thought to be approximately twice as prevalent in females as in males (Niebuhr, 1978; Van Buggenhout *et al.*, 2000; Dykens *et al.* 2000). There is some evidence that prenatal screening can be used to detect CdCS. (Tan *et al.*, 2023; Sivakumar & Balayla, 2024; Chu *et al.*, 2022; Li *et al.*, 2021)

Genetics and Molecular Biology

CdCS is predominantly caused by a partial deletion on the tip of the short-arm of chromosome 5 (with a critical region of 5p15). The size of the deletion ranges from the entire short arm to the region 5p15 (Overhauser *et al.*, 1994). A de novo deletion is present in 85% of cases; 10 to 15% are familial with more than 90% due to a parental translocation and 5% due to an inversion of 5p (Van Buggenhout *et al.*, 2000). Niebuhr first identified the specific chromosomal region implicated in the syndrome as 5p15.1-5p15.3, using cytogenetic analysis (Niebuhr, 1978). More recent work has mapped specific critical areas within this region as being responsible for the expression of the core clinical features of the syndrome. For example, the characteristic high pitched 'cat-like' cry from which the syndrome derives its name has been mapped to the proximal part of 5p15.3, the speech delay to the distal part of 5p15.3 and severe intellectual impairment to 5p15.2 (Overhauser *et al.*, 1994). This distinctive cry is considered the most prominent clinical diagnostic feature of the syndrome (Mainardi *et al.* 2006). Though relatively rare, CdCS represents the most common deletion syndrome in humans (Cornish *et al.* 2001). DNA methylation changes have been identified in those with CdCS

(Holland *et al.*, 2022) and may effect gene modulation therefore explaining phenotypic variability in CdCS (Almeida *et al.*, 2024)

Physical features and natural history

The distinctive cat-cry is a core feature of the syndrome and is still regarded as an important early clinical diagnostic feature in most but not all individuals (Mainardi *et al.*, 2006), with this developing into a higher pitched voice later in life (Sforza *et al.*, 2024). The cry is thought to be caused by anomalies of the larynx (small, narrow and diamond shaped) and of the epiglottis that is usually small and hypotonic (Niebuhr, 1978). It has however been found that oral stimulation interventions in newborns with CdCS are beneficial to their development, improving oxygen saturation and preventing hypoxia, which shortens hospital stay at the beginning of life (Kim & Kim, 2018). Many infants tend to be of low birth weight and low weight usually persists in the first two years of life for both sexes (Marinescu *et al.*, 2000). Feeding difficulties are common and the associated failure to thrive may be the initial clinical presentation. Some infants may require tube feeding, a process which may have to continue for several years. Gastroesophageal reflux is common in CdCS during the first years of life. Congenital heart defects are a common health concern for those with CdCS with a 36% prevalence, as well as being one of the most common causes of death for those with CdCS (Nguyen *et al.*, 2015) Other health problems include respiratory tract infections, otitis media and dental problems. Many individuals with CdCS are prone to developing a curvature of the spine (congenital scoliosis) and this can become more apparent with advancing age. Some of the most frequently cited physically defining features of CdCS are facial characteristics including microcephaly, rounded face, widely spaced eyes, downward slanting of palpebral fissures, low set ears, broad nasal ridge and short neck (Dykens *et al.*, 2000; Marinescu *et al.*, 1999). Studies indicate that facial features change over time, specifically, lengthening of the face and coarsening of features (Mainardi *et al.* 2006).

Behavioural characteristics

Sleep difficulties are a significant problem in this group, occurring in between 30 to 50% of individuals (Maas *et al.*, 2009; Xavier *et al.*, 2024). Repetitive behaviours are generally less common in CdCS than in other genetic syndromes. However, Moss *et al.* (2009) report that an attachment to specific objects is a marked characteristic of the syndrome. Occurring at a clinically significant level in over 67% of individuals, the frequency of this behaviour is significantly higher in CdCS than in other genetic syndromes including and in comparison to individuals with intellectual disability of heterogeneous cause. This behaviour differs from that commonly seen in autism spectrum disorder as it is typically focussed on one specific item (as opposed to a class of items) and the item may change over time. Additionally, the behaviour tends to become less marked with age.

Self-injurious and aggressive behaviours are a common behavioural feature of CdCS (Collins & Cornish, 2002; Cornish & Munir, 1998; Cornish & Pigram, 1996; Dykens & Clarke, 1997; Bel-Fenellos *et al.*, 2023). Self-injury is reported to occur in between 70% and 92% of individuals (Arron *et al.*, 2011; Collins & Cornish, 2002; Cornish & Pigram, 1996; Dykens & Clarke, 1997). The most common forms of SIB are reported to be head banging, hitting the head against body parts, self-biting, rubbing or scratching self (Arron *et al.*, 2011; Collins & Cornish, 2002). Aggressive behaviour has been reported in between 52% and 88% of individuals with CdCS (Arron *et al.*, 2010; Cornish & Pigram, 1996; Collins & Cornish, 2002) with an odds ratio of 2.7 compared to a matched contrast group (Arron *et al.*, 2011). The most common topographies are reported to be hitting, pulling hair, biting and pinching (Collins & Cornish, 2002).

Hyperactivity is a commonly reported feature of CdCS. Findings vary from reports of no increase in level of activity (Baird *et al.* 2001) to 90% prevalence rates of hyperactivity (Cornish *et al.* 1998) with clinical hyperactivity (ADHD) reported to be more prevalent in CdCS than in an intellectual disability comparison group (Cornish & Bramble, 2002). The available literature documents the contrast between high prevalence of Attention Deficit Hyperactivity Disorder (ADHD) and the commonly identified

immobility and severe motor delay (Cornish & Bramble, 2002). The reported high prevalence of ADHD like phenomena has raised concerns regarding both the restrictions this may place on cognitive and emotional development (Cornish *et al.*, 1998) and its role in determining familial stress (Cornish & Bramble, 2002). This highlights a need to clarify prevalence as recommendations are often made for a relatively low threshold for medication in treating hyperactivity in these individuals (Dykens & Clarke, 1997) even though there is some evidence identifying intensive behaviour modification as the most effective intervention (Wilkins *et al.*, 1983).

ASD characteristics are not considered to be strongly associated with the CdCS (Moss *et al.*, 2008; Bozhilova *et al.*, 2023) and have been reported to be less severe relative to a matched control group (Claro *et al.*, 2011). In fact, several studies report social interaction skills as being a relative strength of individuals with CdCS (Carlin, 1990; Cornish & Pigram, 1996). Specifically, Moss *et al.*, (2013) report that communication skills used to solicit social interaction (indicative of social motivation) occurred significantly more frequently in individuals with CdCS relative to matched contrast groups of individuals with Cornelia de Lange and Angelman syndromes during structured social observations. Receptive language was also noted to improve across the lifespan whilst other skills remained stable (Cochran *et al.*, 2019).

Delayed but not deviant speech patterns, particularly in gestural and lexical fields, are also found to be a common characteristic in individuals with CdCS (Kristofferson, 2020). Intelligibility of speech may also be reduced due to difficulty producing consonants (Kristofferson *et al.*, 2014). This is consistent with indications that children with CdCS and difficulties articulating may recall more detailed representations of words than they are capable of expressing (Garmann *et al.*, 2017).

Neuropsychological characteristics

Early reports on CdCS suggested that profound intellectual disability was a common feature of the syndrome (Niebuhr, 1978). More recent, albeit limited, research data indicate that there is a wider range of cognitive ability (Cornish, 1996; Cornish

et al. 1999). Progression in motor development is delayed and adaptive behaviour within the domains of socialisation, communication, daily living skills and motor skills does not appear to show any significant strengths or weakness, although no contrast groups have been employed in research studies (Cornish *et al.* 1998). Marinescu *et al.* (1999) found no association between the size of the genetic deletion on 5p and scores on the Vineland Adaptive Behavior Scales, however Bel-Fenellos *et al.* (2023) found a significant association between the size of the 5P deletion and cognitive levels, with a bigger deletion in all cases resulting in lower scores on cognitive measures. Furthermore, individuals with translocations have been found to have a more severe developmental delay, heightened social withdrawal and more autistic-like features than those with deletions (Dykens & Clarke, 1997; Mainardi *et al.* 2006; Sarimski, 2003).

Useful websites/associations/resources for more information

- www.criduchat.org.uk
- <https://findresources.co.uk/the-syndromes/cri-du-chat>
- Oliver, C., Moss, J., Petty, J., Tunnicliffe, P., Hastings, R., Howlin, P., Griffith, G., Bull, L., Villa, D. and Yip, M. (2009). *Understanding and Changing Challenging Behaviour in Cri du Chat Syndrome*. Aerocomm Ltd: Essex -Available from the CdLS Foundation UK and Ireland.
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Down Syndrome

Originally described by John Langdon Down in 1866 (Down, 1866), Trisomy 21 was first reported in association with Down syndrome by Jérôme Lejeune, Raymond Turpin and Marthe Gautier in 1959.

Epidemiology

Incidence varies globally, in part due to choices surrounding prenatal testing. In the USA, 1 in approximately 800 live born children will have Down syndrome (de Graaf, Buckley, & Skotko, 2015). In Europe there are an estimated 419,000 people with Down syndrome, as of 2015 (de Graaf, Buckley, Skoto, 2021). Ireland has the highest incidence in Europe (1 in 546 live births) (Ni She & Filan, 2014). In England and Wales, approximately 1 in 1000 live born children have Down syndrome (Wu & Morris, 2013) however in Iceland, no infants with Down syndrome have been born during a five year period (Wise, 2016). In India approximately 21,000 babies are born with Down syndrome each year (Verma 2002).

The likelihood of having a child with Down syndrome increases with increasing maternal age: mothers aged 40 are 16 times more likely to have an affected pregnancy than mothers aged 25 (Wu & Morris, 2013).

Life expectancy has increased dramatically over the past 50 years, now reaching approximately 60 years of age (Wiseman *et al* 2015; Coppus 2017). While rare, it is not unheard of for some individuals to live past the age of 70.

Genetics

Down syndrome is caused by a triplication of human chromosome 21 (Hsa21) (Lejeune *et al.*, 1959). This is typically a full or partial trisomy of Hsa21. In approximately 4% of individuals, Robertsonian translocation of the long arm of Hsa21 (generally to Hsa14 or Hsa22) causes Down syndrome. Mosaicism, in which the third copy of Hsa21 is present in some, but not all of an individual's cells, accounts for between 1.3-5% (Flores-Ramírez *et al.*, 2015; Morris, Alberman, Mutton, & Jacobs, 2012; Papavassiliou, Charalsawadi, Rafferty, & Jackson-Cook, 2015).

Excess of genetic material leads to dysregulated expression of certain genes (Letourneau *et al.*, 2014). The functional impact of these changes could be a direct result of the action of the proteins expressed in excess by the Hsa21 genes, or indirectly through the proteins that they regulate. In any case the effect will be different according to the protein involved (Fillat *et al.*, 2014). The nuclear compartments of trisomic cells may also undergo modifications of the chromatin environment influencing the overall transcriptome (Letourneau *et al.*, 2014) and downstream stress-effects stemming from an imbalanced genome are reported (Li, Zhu, 2022).

221 coding, and 447 non-coding genes have been identified on Hsa21 (Ensembl, 2023). It remains a subject of on-going research whether the features and conditions associated with Down syndrome are the result of general dysregulation of the genome caused by the presence of an extra chromosome, or whether they are related to gene-specific over expression.

The development of mouse models of trisomy 21 and induced pluripotent stem cells (iPSCs) has helped to shed light on the role of specific genes on chromosome 21 and their contribution to the Down syndrome phenotype. Models are used to show whether specific genes are necessary and sufficient to cause a certain phenotype.

A number of genes on chromosome 21 have been identified which appear to contribute to the Down syndrome phenotype or development of common health conditions, the most well-researched of these are Amyloid Precursor Protein (*APP*) and dual specificity tyrosine-regulated protein kinase 1 (*DYRK1A*). Other identified genes include Down syndrome critical region 1 (*DSCR1*; also known as *RCAN1*), *BACE 2*, *SOD1*, *S100B*, while polymorphisms in the rest of the genome may also have an impact, such as *GATA1* and its association with leukaemia in children with Down syndrome.

- Triplication of *APP* is the primary driver for early-onset Alzheimer's disease (AD) observed in people with Down syndrome (Wiseman *et al.* 2015). Rare

individuals with Down syndrome who have incomplete trisomy and only two copies of *APP* (disomy) do not appear to have the same AD risk (Doran *et al.*, 2017). Triplication of *APP* leads to increased deposition and accumulation of amyloid-beta protein throughout life. Duplication of the *APP* gene in the absence of Down syndrome is known to be sufficient to cause early onset AD (Slegers *et al.*, 2006).

- *DYRK1A* is particularly expressed in the hippocampus, cortex, cerebellum, and heart—regions and overexpressed in fetal Down syndrome. Transgenic mice that overexpress *DYRK1A* show learning and memory deficits. It has been linked to impairments in angiogenesis and increased risk of developing pulmonary hypertension (Colvin *et al.* 2017). Further, *DYRK1A* phosphorylates tau protein, and this change is known to be important in initiating the cascade of processes leading to AD. When this over-expression is reduced in mice, amyloid-beta and tau levels are reduced, as is cholinergic neurodegeneration (García-Cerro, Rueda, Vidal, Lantigua, & Martínez-Cué, 2017).

Phenotype

Trisomy 21 is associated with a number of common characteristics but there is considerable individual variation. Intellectual disability is present to some degree in all patients with full trisomy 21 but varies from mild disability to severe and profound. Motor dysfunction occurs frequently and individuals with Down syndrome can exhibit clumsy sequences of movements, with poor control of motor sequences, timing and force. Motor dysfunction in people with Down syndrome is accompanied by hyporeflexia and reduced muscular strength and tone (Antonarakis *et al.*, 2020). Most adults with Down syndrome are of short stature (70%), with a characteristic facial appearance. Their eyes slope upwards and outwards as a result of alterations in the structure of the surrounding tissues (“upslanting palpebral fissures”). The nose has a wide bridge, and the head an unusual shape (“brachycephaly”). Protruding tongue is present in 45% of children with Down syndrome. Limb abnormalities

include a single transverse crease on the palm (85%), a large cleft between the first and second toes, and relatively short upper arms.

Physical Health

Many individuals with Down syndrome have significant hearing loss, usually of the conductive type. Sight problems (44-71%) and cataracts are common in Down syndrome individuals, the incidence increasing with age.

Obstructive sleep apnea (OSA) is common in people with Down syndrome, and is increasingly being recognised as an important condition to screen for and to manage. More than 1 in two of people with Down syndrome may have some degree of sleep apnoea. Symptoms include loud snoring, heavy breathing, restless nights and daytime sleepiness, as well as neurocognitive symptoms such as irritability, low mood, and difficulty with focus and attention or behavioral problems. General screening tools based on signs and symptoms may not be adequately sensitive to diagnose OSA and it is suspected that it remains under-diagnosed in this population (Simpson *et al.* 2018).

About half of people born with Down syndrome have congenital heart defects (CHD), most commonly atrioventricular septal defect (42% of CHD in Down syndrome), ventricular septal defect (22%), and atrial septal defect (16%) (Bergström *et al.*, 2016).

Epilepsy is present in 8% of children with Down syndrome, with a bimodal age of onset. One peak is before the age of 3 years, and the other occurs after the age of 30 (Roizen & Patterson, 2003). Infant onset has been associated with West Syndrome. Onset of epilepsy later in life is linked to the development of Alzheimer's disease (Gholipour, Mitchell, Sarkis, & Chemali, 2017).

Bowel problems including duodenal stenosis/atresia (250 times more common in people with Down syndrome) and Hirschsprung disease (30 times more common) occur in babies with Down syndrome, while celiac disease and constipation may be more common in young people and adults, and can be overlooked, particularly in people with more severe intellectual disabilities.

Haematological malignancy, specifically acute megakaryocytic leukemia is 300-times more frequent in children with Down syndrome. Down syndrome is also associated with an increased incidence of autoimmune disorders, such as autoimmune thyroiditis, primary sclerosing cholangitis, celiac disease and alopecia areata (Alexander *et al.*, 2016; Bittles, Bower, Hussain, & Glasson, 2007; Glasson, Dye, & Bittles, 2014). In younger people the incidence of diabetes is up to 4 times that of people without Down syndrome, with onset of both type 1 and type 2 diabetes occurring at younger ages (Aslam *et al.* 2022). People with Down syndrome are prone to disorders of the thyroid gland (15% develop hypothyroidism during childhood or adolescence).

Health conditions associated with getting older, particularly bone disease including osteoporosis, obesity, cataracts, kidney disease and diabetes occur at earlier ages in people with Down syndrome compared to the general population. This includes Alzheimer's disease which is extremely common, with a rate nearly 95 times that of the general population. Other conditions including epilepsy, sleep disorders, and strokes occur around the same time as dementia onset and may be caused by the same disease pathways (Baksh, Pape *et al.* 2023).

On the other hand, people with Down syndrome are less likely to have high cholesterol, high blood pressure, ischaemic heart disease, solid cancers, glaucoma or mental health disorders.

Mental Health

People with Down syndrome have increased incidence of behavioural and mental health problems compared to the general population (Tassé *et al.*, 2016). Psychosis appears to be less common. In people with Down syndrome presenting to mental health services, depression and anxiety disorders are the most prevalent conditions.

An increasingly recognised condition is Down syndrome regression disorder. Adolescents and young adults present with loss of skills and independence compared to their previous levels of functioning. There is often withdrawal from activities and up to 90% of people show language regression. Features can appear similar to catatonia including stereotypes,

reduced volition and psychomotor slowing. It is estimated that around 50% of people make a partial or full recovery, with 35% stabilising at a poorer functioning level (Santoro *et al.*, 2020). At present the cause of this decline is unknown, although it has been suggested that the decline can occur after exposure to emotional stressors (Mircher *et al.*, 2017). An inflammatory or autoimmune aetiology has been suggested. There is often a poor response to antidepressant and antipsychotic medication. Electro-convulsive therapy, steroids and intravenous immunoglobulins have been trialled with some success in subgroups of individuals, but many individuals do not fully recover.

Behavioural characteristics

Fewer behavior problems compared to controls with cognitive disability have been described in people with Down syndrome, but are more frequent than in sibling or in controls without intellectual disability. Children with Down syndrome may be at a lower risk for significant behavioral difficulties in that they show a lower profile of problem behaviors compared to children with other intellectual disabilities. However, in comparison to typically developing age-matched peers, children with Down syndrome can show higher rates of inattention and impulsivity (which may be associated with ADHD), and oppositional behaviors (Dykens, 2007).

People with Down syndrome may present with autism spectrum disorder (~10-15%) and attention deficit hyperactive disorder (ADHD ~6%). Clinical presentations may differ from the general population and assessments may require input from specialists. They may also present with conduct/oppositional disorder (5-4%), or aggressive behaviour (6-5%). The stereotype of people with Down syndrome as happy, placid individuals with a gift for mimicry is therefore not always borne out by behavioural research. "Stubbornness" and obsessional features seem to be relatively common, and many people with Down syndrome react adversely in situations involving conflict.

No significant associations between age and the range or severity of any behavioural and emotional items were found in adults with Down syndrome

without dementia. This suggested a more positive pattern for ageing adults with Down syndrome until symptoms of dementia develop (Makary *et al.*, 2014), although depressive symptoms have been described prior to dementia onset.

Cognitive characteristics

Intellectual disability is present in almost all people with Down syndrome, but with individual ability varying widely, from borderline to profound (Karmiloff-Smith *et al.*, 2016). Most children and adults with Down syndrome function in the mild or moderate range of abilities, and cognitive abilities tend to be higher among people with mosaicism (Papavassiliou *et al.*, 2015).

Early language milestones, such as babbling, are typically met within a similar period to typically developing infants. However, by school age a specific impairment in expressive language is evident in relation to most individuals' receptive language abilities (Grieco *et al.*, 2015). A distinct cognitive profile is described with particular weaknesses in processing verbal information (thought to be secondary to phonological loop deficits) and executive function, especially related to attention, processing speed, verbal working memory and set-shifting. Individuals with Down syndrome show particular difficulties with inhibition but in terms of planning, for example, may take longer than mental-age matched controls, but can achieve similar levels of performance (Grieco *et al.*, 2015). Relative strengths are observed in non-verbal learning and memory (Hamburg *et al.* 2019; Lanfranchi *et al.* 2010).

There is increasing evidence that obstructive sleep apnoea, and disrupted sleep in general, may contribute to some of the cognitive problems experienced by people with Down syndrome (Breslin *et al.*, 2014; Chen, Spanò, & Edgin, 2013; Esbensen & Hoffman, 2018).

Alzheimer's disease and dementia

In adults with Down syndrome, brain changes typical of Alzheimer's disease (AD) usually develop by the fourth decade of life, and dementia is now considered to be the leading underlying cause of death in older adults with Down syndrome (Hithersay *et al.*, 2018).

Intra-neuronal amyloid-beta deposition starts as early as the first decade, with extra-cellular diffuse plaques observed in adolescents with Down syndrome (Fortea *et al.* 2021). On post-mortem examination, almost all adults with Down syndrome over the age of 35 have the brain changes characteristic of Alzheimer's disease (i.e. amyloid plaques and neurofibrillary tangles) (Mann & Esiri, 1989; Wisniewski, Wisniewski, & Wen, 1985).

Adults with Down syndrome are much more likely to develop dementia of Alzheimer type than the general population, with cumulative risk estimated to be in excess of 80% by age 65 (McCarron *et al.*, 2017). However, age of dementia onset shows considerable variability. The average age of dementia diagnosis is typically in the mid-50's, yet a small number of individuals are reported to show decline before the age of 40, and several individuals live in to their 60's with their cognitive abilities relatively well preserved (Hithersay *et al.*, 2018; Sinai *et al.*, 2018). Further research concerning the factors that drive such variability is required, however it has been shown that earlier diagnoses are seen in those with early-onset epilepsy, and multiple health-comorbidities (Hithersay *et al.*, 2018), and for women with Down syndrome, earlier dementia onset is associated with earlier menopause (Coppus *et al.*, 2010).

While there is a clear association with *APP* and AD in Down syndrome (see above), non-chromosome 21 genes that are known to influence dementia onset in sporadic AD, such as *APOE*, assert a similar influence in Down syndrome (Hithersay *et al.*, 2018; Lai *et al.*, 1999). Further, experimental studies have confirmed that triplication of genes on Hsa21 increase amyloid-beta deposition and cognitive deficits independently of *APP* (Wiseman *et al.*, 2018).

Clinical signs and symptoms of AD in Down syndrome include early changes in memory and attention (Firth *et al.*, 2018; Startin *et al.*, 2019). Executive functioning, behavioural and personality changes may also be seen (Ball *et al.*, 2006; Dekker *et al.*, 2015; Lautarescu, Holland, & Zaman, 2017). The prodromal phase of Alzheimer's disease may present with depressive symptoms or behavioural and personality changes creating a potential diagnostic challenge for clinicians.

Baseline cognitive assessments are essential for tracking subtle changes in cognition at the earliest stages. Direct cognitive assessments are able to detect change before caregivers may be aware of any decline (Startin *et al.*, 2019).

As dementia advances, neurological features become more apparent, with incontinence and Parkinsonian traits commonly seen (Strydom *et al.*, 2010). Late-onset seizures develop in more than 40% of individuals with Down syndrome and AD, with seizures starting a median of 2-years after dementia diagnosis. Seizure development is associated with more rapid cognitive decline. In later stages, individuals will lose their ability to walk and talk and eventually become unresponsive.

In any adult for whom the diagnosis of Alzheimer's disease is being considered, a complete medical assessment should be done to detect any treatable disorders such as thyroid disease or depression.

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Fetal Alcohol Syndrome/ Alcohol Related Neurodevelopmental Disorder/ Fetal Alcohol Spectrum Disorders

First description and alternative names

FAS was first observed in Nantes by pediatrician Paul Lemoine in 1968 who described similar dysmorphic facial features and growth delays in 127 infants of pregnant alcohol-drinking mothers. Fetal Alcohol Syndrome (FAS) was coined in Seattle by David Smith and Ken Jones in 1973(1,2). The Institute of Medicine in 1996 delineated Full FAS, Partial FAS, and Alcohol Related Neurodevelopmental Disorder (ARND) based on the presence or absence of facial dysmorphology and /or growth retardation (3). ARND replaced the old term Fetal Alcohol Effect (FAE). FAS Spectrum Disorders, an umbrella term, was introduced by O'Malley & Hagerman in 1998, refined to Fetal Alcohol Spectrum Disorders (FASDs) by Streissguth & O'Malley in 2000 (4,5). In 2013 DSMV proposed a new diagnostic guideline for those with neurobehavioural disorders associated with prenatal alcohol exposure (NDPAE 315.8) but without facial features. It requires features to be ruled into a diagnosis with other factors ruled out. This was the first time this was included in an international diagnostic manual. In 2016 the Canadian guidance (19) updated their criteria to FASD with and without dysmorphic features. This approach was adopted by the Scottish review and similar approaches were taken in Australia with their own guidance(23). NDPAE is the only approach that really currently allows the diagnosis to be made by a single practitioner rather than a multidisciplinary team.

Genetics and molecular biology

Both FAS and ARND are teratogenic conditions, but recent research is beginning to study the epigenetic effects of prenatal alcohol exposure. For example, the major liver pathway of oxidative metabolism which produces acetaldehyde by cytotoxic alcohol dehydrogenase is also accompanied by a reduction in NAD to NADH. There is a subsequent alteration in the cellular redox triggered by a change in the NAD/NADH ratio which may result in gene activation resulting in a change in gene expression. Increasingly the impact of prenatal alcohol on epigenetic mechanisms has

also been investigated. For example, studies have demonstrated that prenatal alcohol exposure has the ability to modify methylation of the retrotransposon prior to the AVY gene in genetically inbred mice, leading to differences in coat colors (17). A wide range of mechanisms beyond this have been identified, from direct apoptotic damage, interneuronal signaling deficits and damage to scaffolding proteins interfering with neural migration (18). The interface between direct and indirect effects lead to a complex presentation with over 428 different presentations and comorbidities being found to be linked to FASD (37,38)

Incidence/ prevalence

The recognition and incidence for FAS has been shown to be increasing. Original estimates varied from 3 per 1,000 live births in the USA to 40 per 1,000 births in South Africa. More recent studies in Lazio, Italy and Cape Town, South Africa, have suggested much higher rates of 35/1000 to 890/1000 respectively (6,10,13). Methodological issues, genetic differences in the susceptibility to alcohol based on the mother's liver metabolism, as well as differences in population drinking patterns may account for some of the variance(7). As a result, whilst the exact incidence for any one population differs greatly and is unknown the rates are considered. In recent years two international systematic reviews of the epidemiological literature identified rates internationally (21,22). Rates varied across the world with high risk populations such as those in care or in prison or in the looked after children's population being exponentially affected(28,29). A review in America identified from active ascertainment studies a rate of around 5% (20) and more recently an estimate of prevalence from a longitudinal cohort study in the UK suggested rates of anywhere between 6-17%(24). This was followed up by an active ascertainment prevalence study completed in schools around Manchester. This demonstrated prevalence rates of between 2 and 4% (31). These rates suggest even at lower estimates this is far from a rare disorder.

Physical features and psychiatric characteristics

Characteristic facial features include short palpebral fissures, thin (flat) upper lip, flattened philtrum, flat midface. Growth retardation less than the 10th percentile for height and weight. Low birth weight for gestational age, decelerating weight over time not due to nutrition, disproportional low weight-to-height ratio. FAS has the classic facial features, ARND does not have the facial features. Increasingly however with the use of newer technologies such as 3d facial mapping the landmarks that were described as associated in the past are becoming much easier to quantify and measure. Features such as flat midface and micrognathia are increasingly possible to quantify against normal populations and are being seen more commonly, even when classical facial stigmata are absent(25).

Gross and fine motor delays as in Developmental Coordination Disorder. Alcohol Related Birth Defects (ARBD) with eye, renal, cardiac and/or skeletal anomalies. FAS is the much less common, but most recognizable form of FASD (3,8,9,10). Infants can demonstrate Primary Regulatory Disorders characterized by difficulties in tolerating environmental stimuli (i.e. habituation problems), coordinating basic motor movements (i.e. sucking), or interacting with parents or care-providers. Secondary psychiatric disorders appear due to environmental stressors such as PTSD after physical or sexual abuse, or Reactive Attachment Disorder of Infancy or Early Childhood related to separation from birth mother or multiple foster home placements. Emerging evidence however, would suggest that the neurodevelopmental consequences of FASD for outcomes such as ADHD and ASD are independent of postnatal factors(27).

FASD increases the vulnerability to many common psychiatric disorders, such as ADHD, Mood Disorder, Anxiety Disorder, Alcohol or Drug Dependence, PDD, Autism and Schizoaffective Disorder. Personality Disorders seen are, Avoidant, Dependent, Schizoid, Passive/Aggressive and Borderline. Presence or absence of facial dysmorphology or growth features do not clinically correlate with the psychiatric presentation or structural brain damage in FASD (5,8, 11, and 12).

Neuropsychological Deficits

70-75% of patients with FASD do not have intellectual disability. The neuropsychological profile consistently shows a Complex Verbal and Non-Verbal Learning Disorder affecting multiple domains of functioning including attention, impulsivity, working memory, executive function, processing speed, social skills, interpersonal relatedness and language development. It includes a Mathematics Disorder and/ or Disorder of Written Expression and/or Reading Disorder, and evidence of a Mixed Receptive/ Expressive Language Disorder with specific deficits in social cognition and social communication. Vineland Adaptive Behavioral Scale (VABS) shows Functional Deficits in daily living skills, socialization and communication. Those with higher functioning in some areas can often mask their difficulties until external pressures lead to higher level abilities such as executive functioning being less effective. Simple functions are often intact. For example, an individual can sequence and switch separately but not when these two tasks are combined. Working memory deficits tend to be verbal working memory deficits rather than numerical having implication as to how these skills are tested. (3, 5, 8,9,10, 13).

Brain structural abnormalities

Autopsy reports of infant deaths and MRI studies showed diffuse structural brain changes. These include hydrocephalus, microcephaly, corpus callosal agenesis, cerebellar hypoplasia, enlarged ventricles and heterotopias (8, 9). Brain imaging studies consistently show microcephaly. The corpus callosum is most commonly affected. The basal ganglion caudate and the hippocampus, integral in working memory and executive function, may be decreased in shape and volume, and the cerebellum may be smaller (5,9,14).

Brain neurotransmitter and neurophysiological abnormalities

Diffuse CNS neurotoxic effects include cell death and/or disruption of cell migration, proliferation, differentiation and maturation (3,5, 8, and 9). Deficits have been discovered in all neurotransmitter systems. Dopaminergic and noradrenergic deficits are likely connected to ADHD presentation of FASD (4,12,15). EEG abnormalities show infant/ child cerebral immaturity,

sleep state EEG, as well as temporal lobe dysrhythmia and complex partial seizure disorder in 6 to 19 year olds with FASD (1,12).

Available guidelines for behavioral assessment/treatment/management strategies

Much of increasing research focus has been shifting to interventional research. Around the world there have been various studies looking at how to support individuals, how to assess and manage them but also what pharmacological and psychological approaches are most effective. Whilst randomised control trials remain limited and rare in this field, they are increasing. A review conducted highlighted some of the more recent developments in psychological and psychotherapeutic interventions as well as increasing developments in psychoeducational approaches to help support basic functions of the condition (42). Further work continues to develop. For example, using positive behaviour support as a mode of intervention (30).

Further focus on comorbid psychological trauma and the impact of environmental influences as a compound effect on behavioural presentation has increased (32,35,39,40). Linked to this is more interventional research around parenting support to help prevent the development of compound trauma in these individuals (36, 41)

Medication research remains limited but a series of consensus statements have emerged to guide clinicians (34). These include in areas around general integration of medication and behavioural management, modification of ADHD treatment in those people who have FASD (26) as well as psychotropic medication usage and guidance (33).

Useful websites /associations for more information

- <https://fasd-uk.net/>
- <https://nationalfasd.org.uk/>
- www.fasd.ie
- www.nofas.com
- www.nofasd.org.au

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Fragile X Syndrome and Fragile X-associated Disorders

First described

Martin & Bell (1943): families with sex-linked inheritance for learning difficulties & characteristic physical features. Lubs (1969) identified the chromosome fragile site just above the tip of the X chromosome's long arm. Sutherland (1977) confirmed the importance of a folate-deficient culture in revealing the site. Verkerk *et al.* (1991) described the multiple CGG repeat sequence at Xq27.3 producing local hyper-methylation and impaired protein synthesis of FMRP. This protein is an RNA binding protein that transports mRNAs to the synapse and typically inhibits translation. The lack or deficiency of FMRP in fragile X syndrome causes enhanced translation of many proteins important for synaptic plasticity and other functions in the CNS. FMRP regulates the translation of hundreds of proteins many of which are important for synaptic plasticity and are associated with autism spectrum disorder (ASD). Fragile X syndrome is the most common inherited cause of intellectual disability and the most common single gene cause of ASD. Therefore, all individuals with intellectual disability or ASD should have fragile X DNA testing if the etiology is unknown. In fragile X syndrome there is enhanced metabotropic glutamate receptor 5 (mGluR5) activity leading to enhanced long term depression (LTD). There is also down-regulation of the GABA system and dysregulation of the dopamine system. Levels of cAMP are low in those with fragile X syndrome. Targeted treatments have been developed to reverse some of the neurobiological abnormalities of fragile X syndrome and are currently being studied in patients with fragile X syndrome.

Genetic aspects

There is sex-linked transmission because the *FMR1* gene is on the bottom end of the X chromosome (Xq27.3), so males are affected more severely than females. There is an expansion of the CGG repeat in the promotor region of the *FMR1* gene through the generations but progression to a full mutation (>200 CGG repeats) only occurs when it passes through a woman to the next generation. Ninety percent of

males with a full mutation (>200 CGG repeats) have intellectual disability and the rest have learning and/or emotional problems. When the CGG repeat in the promotor region of *FMR1* is greater than 200 there is typically methylation of the *FMR1* gene. However, those males with fragile X syndrome who are high functioning (IQ>70) are mosaic (some cells with the premutation (55 to 200 repeats) or partially/completely unmethylated so that some FMRP is produced. In females with fragile X syndrome there is one X chromosome that is normal and the second X chromosome with the full mutation. In these females approximately 25% have intellectual disability and an additional 60% have learning difficulties particularly in math, attention and impulsivity. Some females with the full mutation have no intellectual disability and very few clinical problems and these individuals usually have a favorable activation ratio, meaning the majority of their cells have the normal X as the active X as measured in blood. The diagnosis of fragile X syndrome is made by *FMR1* DNA testing. Cytogenetic studies may also show the fragile site in folate deficient media, but DNA studies are essential for diagnosis and to identify the CGG repeat expansion number. More recent whole genome and whole exome studies have documented point mutations and deletions in *FMR1* that can lead to a fragile X syndrome phenotype without the CGG expansion because the FMRP is abnormal or partially deleted.

Carriers have a premutation and are typically unaffected cognitively, although in approximately 10 to 20% intellectual disability or ASD can occur, particularly in males. Carriers have an elevation of their *FMR1* mRNA level of 2 to 8 times the normal range. This elevation of mRNA leads to a gain-of-function toxicity that can be associated with medical or emotional problems. Primary ovarian insufficiency (menopause before age 40) occurs in 16 to 20% and it is termed fragile X-associated primary ovarian insufficiency (FXPOI). The neuropsychiatric problems occur in approximately 50% and they can include anxiety, depression, insomnia, chronic fatigue, fibromyalgia or chronic pain disorder and these

problems are covered by the umbrella term fragile X-associated neuropsychiatric disorders (FXAND). Additional medical problems that can occur in carriers to a greater extent than age matched controls includes hypertension, migraine headaches, insomnia, sleep apnea, hypothyroidism, gastroesophageal reflux, immune mediated problems, chronic fatigue, fibromyalgia and neuropathy. These problems can be characterized as fragile X-associated conditions (FXPAC) and the psychiatric problems in FXAND that do not meet the DSM5 criteria for a disorder can be labeled as FXPAC.

The most severe neurological problem in a subgroup of aging male and female carriers is called the fragile X-associated tremor/ataxia syndrome (FXTAS). FXTAS is defined as intention tremor, cerebellar ataxia, neuropathy combined with memory and executive function deficits. FXTAS is associated with global brain atrophy and white matter disease, often in the middle cerebellar peduncles, splenium, insula, pons and/or periventricular areas. FXTAS occurs in approximately 40% of older male carriers and 8% to 16% of older female carriers. FXTAS only occurs in premutation carriers because they have elevated *FMR1* mRNA levels which lead to toxicity in the neurons and glial cells; intranuclear inclusions form in the neurons and astrocytes and also in the peripheral nervous system and even in some organs. The FXTAS inclusions have the *FMR1* mRNA combined with proteins that are sequestered by the elevated mRNA. An abnormal protein FMRPolyG is also thought to be formed in those with FXTAS because of RAN translation meaning abnormal translation that does not start at the normal AUG start site but instead upstream, therefore causing the production of the FMRP that has a polyglutamine tail. There are other pathological mechanisms that can lead to neurodegeneration in those with FXTAS including mitochondrial dysfunction and calcium dysregulation in neurons.

Incidence/Prevalence

The allele frequency of the full mutation is 1 in 4000 to 6000 in the general population, however some individuals with the full mutation especially females do not have intellectual disability, although their learning difficulties and emotional problems still constitute

fragile X syndrome. The premutation is more common and 1 in 130-250 females and 1 in 250-800 males in the general population have the premutation. Some parts of the world including Colombia, Israel and Mallorca have a much higher prevalence of the premutation and the full mutation likely related to founder effects.

Institutionalized individuals with intellectual impairment of unknown origin have rates of fragile X syndrome ranging from 2.5% to 5.9%. Fragile X syndrome is the most common inherited cause of learning disability or intellectual impairment and many families have multiple individuals affected by the fragile X mutation. Approximately 2 to 6% of those with autism have fragile X syndrome and it is the most common single gene associated with autism. For males with fragile X syndrome about 60% have ASD but in females only 20% have ASD,

Physical Features in Fragile X Syndrome

Prominent ears are seen in 60% of children and adults usually have a long face and sometimes a prominent jaw. A high arched palate is seen in the majority and strabismus is present in up to 30%. Macroorchidism or large testicles are a feature in adolescence in over 90% of males. A connective tissue dysplasia produces joint laxity particularly hyperextensible finger joints, soft velvety skin and flat feet with pronation. This connective tissue problem can also cause aortic dilatation and/ or mitral valve prolapse, sometimes in adults. Seizures occur in approximately 16 to 20% and recurrent otitis media occurs in the majority in early childhood.

Life expectancy/Natural history

Those with fragile X syndrome have a normal life expectancy except for those who have seizures since death can occur during a seizure rarely. Rare cases of sudden death have been reported in childhood or adulthood. Aging studies in individuals with fragile X syndrome have documented a high rate of Parkinsonian symptoms in the 50s and older which can be exacerbated by the use of antipsychotics in older adults with fragile X syndrome.

Behavioural characteristics

Intellectual impairment is variable and correlates with the molecular findings. Those with higher levels of FMRP, such as females and those with an unmethylated full mutation or mosaic status (some cells with the premutation and some with the full mutation), will have a higher IQ because they are producing more FMRP. Verbal intelligence usually exceeds performance abilities in both affected males and non-learning disabled female carriers, although about 10% of patients will be non-verbal or will have very low verbal abilities. Particular difficulties with numeracy, visuospatial skills and visual motor abilities are common. The rate of intellectual development diminishes with age, particularly after puberty. This will lead to a lower IQ overtime, although there is no regression of abilities but instead a lack of abstract reasoning development which holds the IQ lower with age.

Speech & language development is almost always delayed with dysfluent conversation, incomplete sentences, echolalia, palilalia and verbal perseverations. There is often a jocular quality to speech with narrative, compulsive utterances and swings of pitch ("litany-like"). "Cluttering" refers to the fast and fluctuating rate of talking with marked and frequent repetitions, garbled and disorganized speech, poor topic maintenance, and tangential comments.

Social impairments, ASD, ADHD and social anxiety with aversion to eye contact are present in the majority of children and adults with fragile X syndrome. Approximately 60% of men will have an autism spectrum disorder (ASD). The rest are socially responsive and affectionate individuals with good understanding of emotions, although autistic like features such as perseverations, hand flapping and poor eye contact with shyness are seen in the majority. Self-injury, notably hand biting and aggression provoked by frustration, anxiety and excitement are common. Hand flapping is seen in the majority both with and without autism. Obsessive and compulsive features are common and often lead to rituals and picky eating habits. Mouth stuffing, tactile defensiveness and overreaction to sensory stimuli leading to hyperarousal and tantrum behavior are seen in the majority. Approximately 30% of males have

aggression; and anxiety associated with hyperarousal is a component of this aggression. Individuals with fragile X syndrome have a GABA (inhibitory) deficit and this leads to a lack of habituation to sensory stimuli both in electrodermal studies and also in fMRI studies. The lack of habituation to sensory stimuli in the CNS is correlated to the severity of ASD in females. Hyperactivity is seen in about 80% of boys although attention problems and impulsivity without hyperactivity can be seen in 40% of girls with the full mutation.

Treatment

Individuals with fragile X syndrome typically respond well to a stimulant medication after 5 years of age. Clonidine or guanfacine have been helpful for hyperarousal and hyperactivity in children under 5yo or older. Selective serotonin reuptake inhibitors (SSRIs) help anxiety and can be used even in those under 5, although activation can be seen in about 20%, requiring a lowering of the dose or discontinuation. Atypical antipsychotics, most notably aripiprazole, when used in low dose helps to stabilize mood, decrease aggression, improve attention, and decrease anxiety. Minocycline is a targeted treatment for fragile X because it lowers matrix metalloproteinase 9 (MMP9) levels and a controlled trial demonstrated efficacy in young children with fragile X syndrome, however this can cause darkening of the teeth when started before age 8 so it is rarely used currently. Metformin, a type 2 diabetes drug also lowers MMP9 and it also down regulates the mTOR pathway that is too high in those with Fragile X syndrome so it is also considered a targeted treatment. Metformin has rescued the fragile X phenotype in animal models and it is now undergoing a controlled trial in children ages 6 to 45yo at three centers. Anecdotal cases have demonstrated a benefit from metformin treatment in language skills and behavior and when started before puberty it can decrease the macroorchidism that typically develops.

Arbaclofen, a GABA_B agonist has also been shown to benefit patients with fragile X syndrome particularly those with ASD or social deficits although a controlled trial in adolescents and adults did not show efficacy. However, limited efficacy is seen in younger children ages 5 to 11 treated with arbaclofen. The metabotropic

glutamate receptor 5 (mGluR5) antagonists have not demonstrated efficacy in adolescents or adults with fragile X syndrome in controlled trials and a more recent FXLEARN trial involving AFQ056 plus parent implemented language intervention (PILI) in children ages 3 to 6 did not demonstrate efficacy. A controlled trial of low dose sertraline (2.5 to 5.0 mg) in children ages 2 to 6yo with fragile X syndrome demonstrated efficacy in developmental profiles and is often used clinically. A multicenter trial of a topical ointment with cannabidiol (CBD) underwent a controlled trial at multiple centers to target anxiety in 3 to 18 yo children and it demonstrated efficacy compared to placebo in the social avoidance subtest of the Aberrant Behavior Checklist FX. However, the efficacy was significant only in those with a full mutation that was at least 90% methylated so a second trial is being carried out in multiple centers currently in an effort to gain FXA approval.

An exciting new study has shown that an inhibitor of phosphodiesterase 4D (PDE4D) which inhibits the enzyme that metabolizes cAMP, thus allowing cAMP to rise to normal levels, can improve several aspects of cognition in 30 adult males with fragile X syndrome. This controlled trial excited the interest of families and researchers worldwide so currently further phase 3 controlled trials in adolescent and adult males with fragile X syndrome are taking place. These studies will likely lead to many more treatment options for those with fragile X syndrome and some of the targeted treatments may improve language and cognition in this disorder. The future also looks bright for gene therapy for fragile X syndrome and FXTAS and hopefully clinical trials will begin in the next few years.

Resources

- **The Fragile X Society**, The Chestnuts, 4 Stortford Rd, Great Dunmow Essex. CM61DA, UK. info@fragileX.org.uk. Phone 01371875100
- **The National Fragile X Foundation**, 1012 14th st NW suite 500, Washington DC, 20005, USA. 800-688-8765
- **FRAXA Research Foundation**, 45 Pleasant St., Newburyport, MA 01950, USA. 978 – 462 – 1866

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Klinefelter Syndrome (47,XXY)

First description and alternative names

Klinefelter Syndrome" or "Klinefelter's Syndrome," sometimes abbreviated as KS, was first described by Dr. Harry Klinefelter in 1942 as an endocrine disorder characterized by small testes, hypogonadism, gynecomastia, and increased levels of follicle-stimulating hormone. Patricia Jacobs determined in 1959 that the clinical phenotype was due to a 47,XXY genotype (rather than the neurotypical 46,XY).

Genetics and molecular biology

47,XXY (KS) is a chromosomal variation in males in which one extra X chromosome is present, resulting in an XXY karyotype. 47,XXY (KS) is not inherited. The additional X chromosome arises from non-disjunction either during germ-cell development or in early embryonic cell divisions. Approximately 50% of non-disjunctions appear to be of maternal origin (Iitsuka *et al.*, 2000). The cause of the non-disjunction is not known.

Some cases of 47,XXY (KS) may have 46,XY/47,XXY mosaicism, which is when some of the cells have the 46,XY karyotype and some have the 47,XXY karyotype. Mosaic 47,XXY occurs because of an error in the division of the sex chromosomes in the zygote after fertilization. Mosaicism is not associated consistently with milder presentation in neurodevelopment. Although the higher the presence of mosaicism of 46,XY, the more likely of a milder presentation developmentally.

Incidence/prevalence

47,XXY (KS) is the most common sex chromosome disorder and is currently estimated to affect approximately 1:400 to 650 males. 47,XXY (KS) is an underdiagnosed condition, as only 25% of all cases are detected in their lifetime. Of those diagnosed, it is estimated that less than 10% of cases were diagnosed before puberty (Bojesen & Gravholt, 2007).

However, diagnosis of 47,XXY (KS) through prenatal detection may be increasing through advances in prenatal screening such as non-invasive prenatal screening (NIPS) with confirmatory prenatal

(amniocentesis or chorionic villus sampling) or postnatal (chromosomal microarray or chromosome karyotype) testing. A chromosomal microarray (CMA) test consists of a blood sample or oral cheek (buccal) swab. Cheek swabs are an easy and painless way to detect abnormalities of chromosome numbers to provide a definitive diagnosis.

Physical features and natural history

Although 47,XXY is associated with a characteristic pattern of physical differences, the degree to which an individual is affected varies widely. Males with 47,XXY have been traditionally described as tall, with narrow shoulders, broad hips, sparse body hair, gynecomastia, small testes, and androgen deficiency. However, with testosterone replacement many physical features such as sparse body hair and gynecomastia may be mitigated. Post-pubertal males may manifest infertility, gynecomastia, lack of complete pubertal virilization, testicular failure, azoospermia and elevated gonadotropin levels, with decreased 17-ketosteroid levels. Studies investigating the efficacy of targeted administration of male hormones (androgens), such as testosterone enanthate, in boys with 47,XXY have shown hormone replacement to alleviate feminization effects that may have occurred due to insufficient testosterone levels, while also promoting the development of secondary male sexual characteristics. During adulthood, boys with 47,XXY (KS) are also at increased risk of low energy, low libido, osteoporosis, thromboembolic disease, obesity, and diabetes mellitus when hormonal levels, health and well-being are not well managed. Recently, studies have demonstrated the positive effect of testosterone treatment on the well-being and neurocognitive profiles of boys with 47,XXY (Samango-Sprouse *et al.*, 2013; 2018). Testosterone treatment in boys with 47,XXY has also been shown to decrease anxiety and increase motor proficiency (Samango-Sprouse *et al.* 2013; 2015).

Behavioral and psychiatric characteristics

Individuals with 47,XXY are at increased risk for behavioral problems and psychiatric disorders. Behavioral problems are variable in incidence—although the child with a prenatal diagnosis presents with fewer problems (Ross *et al.*, 2012; Samango-Sprouse *et al.*, 2013; 2015). Additionally, boys receiving early hormonal treatment in infancy or early childhood have fewer behavioural problems than the untreated child or the child postnatally diagnosed (Samango-Sprouse *et al.*, 2015, 2021). School-aged children frequently show problems with anxiety, mood dysregulation, self-esteem, and socialization. Socialization problems frequently relate to social avoidance, secondary to generalized anxiety, and they may become more pronounced during adolescence especially without appropriate hormonal treatment and support. Some of these problems may be exacerbated from frustration stemming from a relatively depressed expressive ability as compared to receptive skills (Simpson *et al.*, 2003; van Rijn *et al.*, 2006). Testosterone replacement therapy may minimize these neurodevelopmental dysfunctions, specifically early hormonal treatment (Ross *et al.*, 2014; Samango-Sprouse *et al.*, 2011, 2013, 2015, 2018, 2021).

Neuropsychological characteristics

Emerging neuroimaging technology has increased and improved our understanding of the relationship among brain development, neurocognition, and behavioral outcome—especially in boys with 47,XXY (KS) (Giedd *et al.*, 2007). Studies on boys with 47,XXY (KS) utilizing these neuroimaging techniques have revealed reduced total brain volumes that are specifically seen in the frontal, caudate, and temporal (especially left) regions of the brain (Giedd *et al.*, 2007). Abnormalities in frontal and caudate brain MRIs are similar to those seen in MRIs of boys with ADHD, and indicative of the executive dysfunction seen in boys with 47,XXY (Giedd *et al.*, 2007; van Rijn and Swaab, 2015). The temporal lobes are associated with language capacities involving reading, social language, and processing of spoken information—all of which are notably challenged in untreated males with 47,XXY (Shen *et al.*, 2004; Savic, 2012). Abnormalities in the caudate nucleus are believed to adversely affect

speech and language, as well as manifest as dyspraxia and oral motor dysfunction that is often found in 47,XXY (KS) boys (Giedd *et al.*, 2007). The gray matter density in the insula region of the brain in these boys is also decreased, which is linked to social and emotional processing issues (Nagai *et al.*, 2007). The parietal lobe, however, is relatively unaffected when measured by cortical thickness and volume (Giedd *et al.*, 2007). The preservation of this region is evident in the enhanced spatial cognitive skills in males with 47,XXY (KS) (Samango-Sprouse and Law, 2001; Savic, 2012). Many 47,XXY (KS) males have normal or above average cognitive capacity with typically higher nonverbal IQs and lower Verbal IQs.

These neuroanatomical findings in 47,XXY (KS) boys have revealed several salient characteristics that are morphologically different from neurotypically developing peers. Several studies, however, have suggested that more normalized brain development is possible through the utilization of hormonal treatment (Patwardhan *et al.*, 2000; Samango-Sprouse *et al.*, 2015). Patwardhan *et al.* (2000) compared two groups of 47,XXY (KS) individuals (one receiving hormonal treatment therapy versus no treatment) and found that temporal gray matter was preserved in the treated group, but diminished in the untreated group. Further studies are warranted to confirm these findings and investigate whether other abnormal brain areas, as described above, show similar normalisation after hormonal treatment therapy.

Available guidelines for behavioural assessments/treatment/management

Once the individual or fetus is diagnosed with 47,XXY (KS), it is important to seek consultation with medical professionals and health care professionals who are familiar with 47,XXY (KS) for recommendations regarding resources, appropriate biological and neurodevelopmental therapies, as well as medications for ADHD or anxiety (Samango-Sprouse & Gropman, 2016). Early interventional therapies (e.g., physical, occupational, and speech therapies) are recommended when discrepancies or deficits are identified throughout early childhood to enhance neurodevelopmental outcomes. Physical therapy is indicated when there is hypotonia, motor delay, and/

or poor coordination and is most effective between 4 and 18 months in order to develop independent ambulation skills. Occupational therapy should be considered for the boys with decreased muscle tone in the trunk or upper body, because these deficits will affect handwriting, posture, attention, and eventual school success. This type of evaluation may be most beneficial between 4 and 6 years of age and typically is needed for 12 months. Additionally, 95% of identified boys with 47,XXY (KS) have reading disorders, which makes many aspects of learning challenging if not properly addressed. Specific speech and language therapies should address speech delays with motor planning deficits, language formulation abnormalities and syntactical delays. Speech therapy should focus on eliminating oral motor weakness and dysfunction through a sensorimotor approach. If there is history of early feeding difficulties with challenges in latching onto the breast or challenges to transitioning to table foods, then an evaluation for tongue and lip ties should be considered. Because of decreased muscle tone and androgen deficiency, an active health style should be encouraged from infancy through adulthood.

Androgen replacement therapy can improve bone density, increase muscle mass and strength, produce more masculine body contour, and decrease body fat. Infants with 47,XXY (KS) experience the neurotypical “mini-puberty” in which testosterone levels surge, though at a significantly reduced rate (Forest *et al.*, 1974, Lahlou *et al.*, 2004). Early hormonal treatment (EHT) may mitigate these testosterone levels and keep these infants on an appropriate neurodevelopmental track (Davis *et al.*, 2019, Samango-Sprouse *et al.*, 2020, 2021). Testosterone can produce adequate pubertal maturation with increased body hair, penile enlargement, and male distribution facial and body hair.

Useful websites/associations for more information

- The Association for X and Y Chromosome Variations (AXYS)
<https://genetic.org/variations/about-47xxy/>
- The Focus Foundation
<http://thefocusfoundation.org/x-y-chromosomal-variations/xxy/>
- Genetics Home Reference
<https://ghr.nlm.nih.gov/condition/klinefelter-syndrome>
- Genetic and Rare Diseases (GARD) Information Center
<https://rarediseases.info.nih.gov/diseases/11920/47-xxy>
- Klinefelter's Syndrome Association UK
<http://www.ksa-uk.co.uk/>
- National Organization for Rare Disorders
<https://rarediseases.org/rare-diseases/klinefelter-syndrome/>

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Lesch-Nyhan Disease (LND)

First Description & History

Historically, Lesch-Nyhan syndrome is the designated term for this disease; however, Lesch-Nyhan Disease (LND) and hypoxanthine-guanine phosphoribosyl transferase (HPRT, HGprt) deficiency are also used to describe this disease.

It is interesting that the first description of Lesch-Nyhan Disease may have been in the year 1267. Beck in 1991, identified an original description of what may be LND when he uncovered several cases of self-injury, gout, and intellectual disabilities in individuals living in a small village in England where St. Thomas, Archbishop of Canterbury, had been killed. The original account, written by Jacobus de Voragine, suggested that the disease might somehow be related to the murder of St. Thomas and the “wrath of God”. We have come slightly further in our understanding of the disorder since then and since the first description of the familial nature of the disease (Nyhan *et al.* 1964, 1965).

Nyhan was the first to describe the familial nature of the disease. His work demonstrated that mutations in the hypoxanthine guanine phosphoribosyl transferase (HPRT) gene, leads to the lack of its enzymatic activity. Dysfunction of HPRT, disrupts the purine metabolism, adversely influencing neurodevelopment and leading to the neurobehavioral phenotypes (Nyhan, 1997) and to an excess of uric acid with many systemic consequences including hyperuricemia, formation of bladder calculi, and painful gouty arthritis. (Torres *et al.* 2007). However, HPRT deficiency results in a broad spectrum of clinical involvement, which depends on the severity of the enzyme deficiency, where an activity of less than 1.5%, is at the severe end of the spectrum. Two less severe variants include HPRT related hyperuricemia, known as Kelley–Seegmiller syndrome which present with an enzymatic activity varying from 8% to 60%, and hyperuricemia with neurological disability, characterized by an enzymatic activity of 1.5-2% with hyperuricemia and neurological symptoms (Nanagiri and Shabbiri 2022). Measurements of blood HPRT activity is still, to date, the gold standard for diagnosing LNS (Nyhan, 2005).

In 1959, two physicians, Catel and Schmidt, described what has turned out to be the first variant of the disorder of partial HPRT deficiency (Kelley-Seegmiller syndrome) which, in turn, involves a variable degree of neurological symptoms without the self-injurious behavior of LND. Two variants of classic LND have been further characterized by Dr. Jinnah and colleagues (2010). These individuals have higher levels of enzyme activity than patients with the classic form and do not have the feature of self-injurious behavior. Elevated levels of uric acid are commonly present in all three types of LND. Seegmiller discovered the enzyme defect in the purine salvage pathway in 1967. Of interest, in 1960, Riley described gout and cerebral palsy in a 3-years old that may be the first classic case of LND in the literature. Hoefnagel *et al.*, in 1965, were the first to suggest it was X-linked. In 1983, Wilson and Kelly identified the first specific mutation at the molecular level: a single nucleotide change in the codon for aspartic acid 193 -- GAC for AAC. This discovery has turned out to be one of many, many different nucleotide changes identified in this gene!

Incidence and Epidemiology

LND is a rare inborn error of metabolism disorder that affects mainly males with an estimated incidence between 1:235,000 and 1:380,000 live births in the US (Torres *et al.* 2007). Studies show that it occurs in relatively equal frequencies in all populations. Because it is an X-linked recessive mutation, it ought to occur only in males, but there have been several documented cases in females – although the lower severity and penetrance can be likely explained by the Lyon hypothesis, so that males who receive from the carrier mothers, the X chromosome carrying the mutated gene, will express the disease while females are mostly carriers but can develop the disease if X chromosome carrying the defective gene is expressed phenotypically.

Genetic aspects

LND is a rare X-linked, recessive genetic disorder caused by a deficiency of hypoxanthine-guanine phosphoribosyltransferase (HPRT) enzyme, located at a q26-27 position on the long arm of the X chromosome (Figure 1).

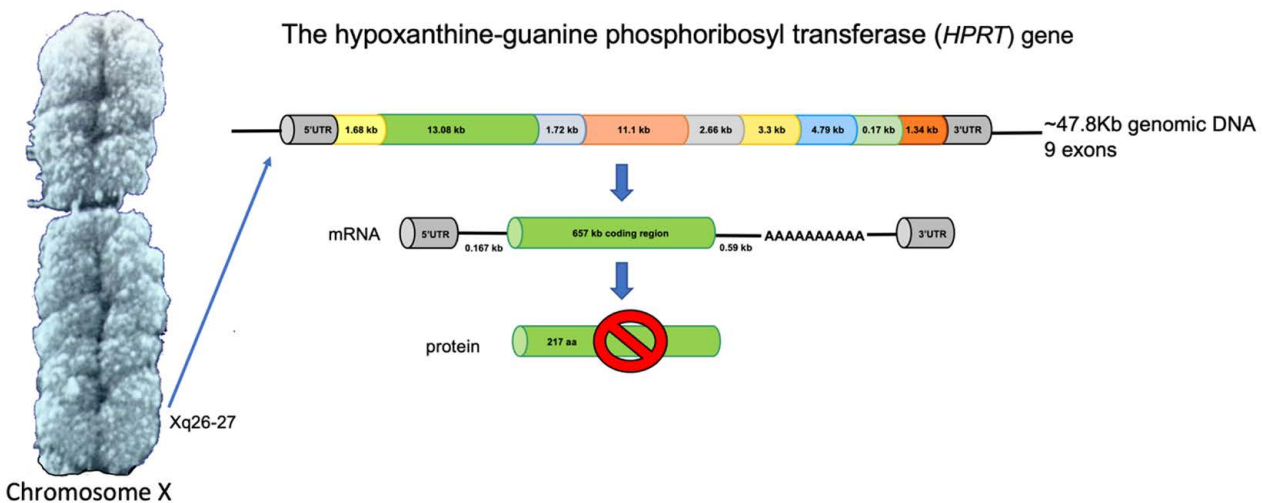


Figure 1. The HPRT gene is located on chromosome X q26-27. It spans approximately 48Kb of genomic DNA and contains 9 exons. The gene encodes for a 217 amino acid protein, which lack of function leads to functional significant purine overproduction and ultimately to neural problems.

The enzyme is a transferase responsible for recycling purines by converting hypoxanthine into inosine monophosphate (IMP) and of guanine to guanosine monophosphate (GMP). This enzyme plays a central role in the generation of purine nucleotides through the purine salvage pathway (Figure 2).

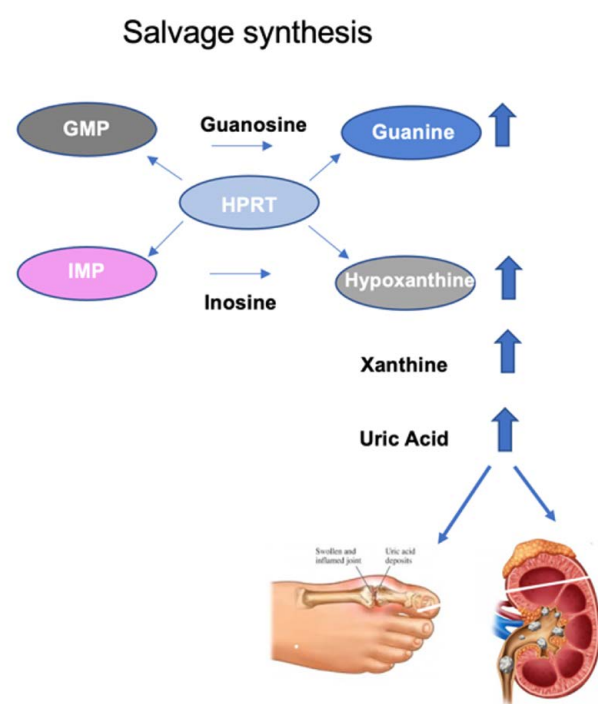


Figure 2. Deficiency of salvage nucleotide synthesis. LND is caused by the deficiency of the purine salvage enzyme HPRT which is responsible for the conversion of hypoxanthine into inosine monophosphate (IMP) and of guanosine into guanosine monophosphate (GMP). After their synthesis they are converted to nucleotides that are used for DNA repair and synthesis. The lack of HPRT also leads to increased uric acid, which accumulation leads to gout and kidney stones.

The significantly reduced or undetectable HPRT activity gives rise to a constellation of symptoms (Jinnah *et al.*, 2006). With an enzyme activity of less than 1.5%, LND falls towards the severe end of the spectrum. The lack of the enzyme causes an increase in guanine and hypoxanthine, which eventually gets converted into uric acid. There are probably a few thousand individuals with this disease in the world. The mutations are within the HPRT1 gene located on the long arm of the X chromosome. Remarkably, over 600 different mutations have been identified

in different families (O'Neill *et al.* 2004), each leading to varying levels of severity of clinical presentations making HPRT enzyme deficiency a spectrum rather than a single disease (Fu *et al.* 2014).

Clinical, cognitive, and behavioural features

LND is characterized by a complex neurological profile which includes generalized dystonia, motor dysfunctions and self-injurious behavior, which management is quite challenging. Individuals with LND are asymptomatic at birth with normal prenatal growth and development. Typically hyperuricemia is present at birth, and orange-colored crystals in the diapers is the only clinical evidence hyperuricemiam, which leads to crystalluria, urolithiasis, nephrolithiasis, gout, and juvenile arthritis. In addition to hyperuricemia, LND is associated with cognitive impairment, renal involvement as well as severe and involuntary self-injurious behaviors.

Although it is appropriately considered a metabolic disease involving the absence, or near absence of the enzyme HPRT, because among other deficits, patients with LND have reductions of dopamine in the basal ganglia, it is tempting to think of this disease as a basal ganglia disorder, even though other areas of the brain are involved as well. From the motor disorder standpoint, LND is best described as dystonia superimposed upon hypotonia, although chorea, spasticity and athetosis have been described. During volitional movements, the examiner may believe increased tone is present, yet when the movement is over or when the patient is relaxed, hypotonia is clear. Further, anxiety often confuses the clinical picture, as it does with other aspects of the disorder, especially when the patient is examined by a physician unfamiliar with the patient. The question of the presence of athetosis vs dystonia and the presence of hypotonia vs spasticity is often difficult to distinguish on exam by a physician who is not familiar with the behavioral manifestations of LND. LND presents in the first few months of life as a developmental delay and may be diagnosed initially as cerebral palsy. Individuals with classic LND are generally non-ambulatory.

The basal ganglia are known to be involved in the regulation of areas other than the motor circuits, including personality, cognition, and emotion (Visser *et al.* 2000).

Although there may be significant bias and scatter, depending on who administers the IQ testing, the range of IQ scores varies but is generally in the mild to moderate intellectual disability range although some authors feel that it is lower, ranging from 40 to 80. The LND behaviors and neurological problems limit the validity of standard IQ tests. Patients with LND can be very engaging and personable and are often able to recount scores of local sporting events on a routine basis. It is interesting that parents often believe IQ scores obtained are artificially low and reason that low performance is secondary to LND behavior.

The behavioral phenotype of LND, physical and emotional self-injury, including severe self-mutilation and aggressive behavior, are generally involuntary in nature, thus, not under the patient's control. These self-destructive behaviors, one of the hallmarks of LND, usually begin between ages three and six and often escalate as the patient ages and the patient is more physically able to cause self-injury. The first manifestations of physical self-injury are lip biting, finger biting, and biting of the oral cavity.

Modes and patterns of self-injury have been previously described in Robey *et al.* and are often specific to each individual patient and appear consistent over the lifespan. Patterns of association involve self-injury to or about: 1) external surfaces or 2) oral or biting, usually of the lips and fingers. If a patient tends to injure him or herself using external surfaces, this pattern tends to continue throughout the lifespan. If the self-injury involves oral cavity or biting, then this pattern will re-occur throughout the lifespan. Forms of self-injury include eye-poking, head banging, fingers in wheelchair spokes, and extension of arms in doorways. Emotional self-injury, or outwardly directed aggressive behaviors, include hitting, kicking, head-butting, biting others, spitting, swearing, ethnic slurs, inappropriate remarks to the opposite sex, frequently changing opinions, and/or lying. When oral self-injury is present, removal of the teeth is essential to prevent facial disfigurement. Decisions regarding dental extraction

must be made with physicians who are expert in the comprehensive care of patients with this disorder (www.Lesch-Nyhan.org).

Treatment

Management of LND syndrome is complex, thus understanding the neurological manifestations of HPRT defect allows for a thorough understanding of the disorder and subsequent comprehensive management strategies.

Since the 1960's we have known that because of the lack of HPRT, there is an over-production of uric acid and subsequent uric acid stone formation, the xanthine urolithiasis (xanthine stone formation is due to dose specific issues of allopurinol.) Allopurinol is a drug that blocks the conversion of hypoxanthine and xanthine to uric acid by inhibiting the xanthine oxidase enzyme, representing the cornerstone of treatment of hyperuricemia. Although Allopurinol is used to lower the elevated serum uric acid, it must be titrated to maintain serum uric acid in the critical window that attenuates the neurologic and systemic consequences of hyperuricemia while avoiding xanthine stone formation. Historically, levels of the serum uric acid have been kept in a range that minimizes the formation of uric acid stones, yet not too low as to lead to the formation of xanthine stones. Unfortunately, treatment of the elevated serum uric acid with allopurinol does not have an impact on the neurobehavioral manifestations of the disease. However, as previously mentioned, since the hyperuricemia is present early during the development, early intervention can avoid many potential complications.

The lack of effective treatment for motor syndrome and featured in LND represents a burden for the patients and also for their caregivers. Treatment for the behavioural manifestations of LND is multi-modal and should include: 1) judicious use of protective devices, 2) utilization of a behavioural technique commonly referred to as selective ignoring with redirection of activities, and 3) occasional use of medications.

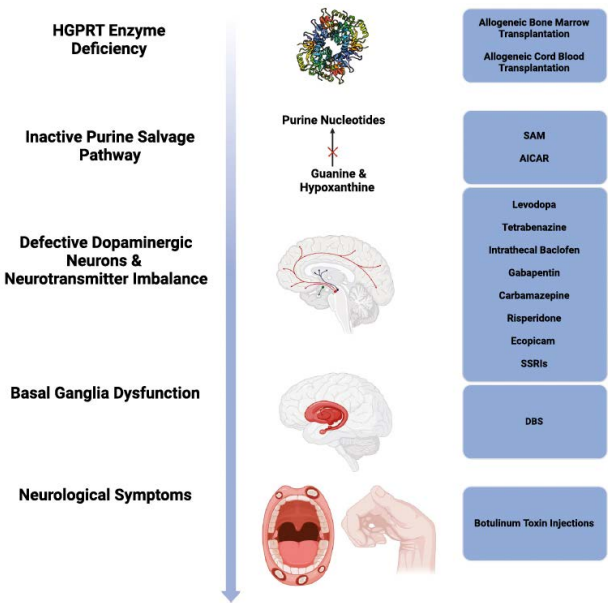
The use of medications for treating the behavioural component of this disorder is controversial yet most children and adults with LND are treated with different medications. No medication has been found

to reverse the so-called 'Lesch-Nyhan behaviours', either motor or behavioural. Selective ignoring is a methodology that is designed to extinguish self-destructive emotional or physical behaviour in the LND patient. It requires the caretaker to ignore such behaviour by the LND patient towards said caretaker so that the behaviour decreases or ceases. Along with selective ignoring, the use of redirection is also found to be helpful. At times controversial, the use of protective devices is essential, yet often problematic for patients and institutions not familiar with the care of LND patients. Professionals unfamiliar with LND may perceive the use of these protective devices from a traditional paradigm of restraints – which is to say, the use of these devices against a patient's will. When protective devices are requested by the patient -- and used to safeguard the patient from him or herself -- the outcome is an extraordinary feeling of comfort and safety. Not allowing the use of protective devices when requested violates the autonomous rights of the patient. In LND self-injury far exceeds that associated with other developmental disabilities, and, of course, is a consequence of the neurotransmitter and cell function abnormalities characterising the disorder. Although not all individuals with this condition demonstrate severe behavioural manifestations, it is reasonable to say that all benefit from the use of protective devices at some point during their lifetime. It is extremely important to note that the Joint Commission and the US government's CMS requirements both include exceptions to the restraint standards for patients with LND.

A recent review reported that Deep Brain Stimulation (DBS) and the use of SAM, S-adenosylmethionine are the two most studied type of intervention (Krajewski *et al.*, 2024). DBS has been tried worldwide in numerous patients with LND as an effective treatment of self-injurious behaviors (SIB) and to decrease the degree of dystonia, although with conflicting results. In this procedure neurosurgeons place two stimulators in the basal ganglia, like the stimulators used in other movement disorders such as Parkinson's disease. The results suggest a decrease in dystonic movements as well as a decrease in self-injurious behavior; however, it is unclear if this will become a standard treatment

option due to variable effects and complications of the surgery. Finally, the use of gabapentin used as a mood stabilizer and antidepressant in LND patients (Jinnah *et al.*, 2006) and botulinum injections have been tried with somewhat a reduced self-abusive behavior ((McManaman and Tam, 1999, Dabrowski *et al.* 2005). Carbamazepine, an anticonvulsant used as a mood stabilizer in neuropsychiatric disorders (Smith, 2005), was tested to determine the efficacy and safety in managing SIB in LND patients, was found to improve behavior in three patients. More details on are reported in a comprehensive review of many studies assessing the efficacy of pharmacological, including Tetrabenazine, Baclofen, Levodopa/Carbidopa, S-adenosylomethionine, 5-Aminoimidazole-4-carboxamide ribonucleotide and more) and non-pharmacological interventions (including Deep brain stimulation, Bone marrow transplantation) in management of neurological symptoms in LND (Krajewski *et al.*, 2024; Figure 3).

Figure 3. Disease mechanisms targeted by reviewed treatment methods of neurological symptoms in Lesch-Nyhan Disease. Abbreviations: AICAR, 5-Aminoimidazole-4- carboxamide ribonucleotide; DBS, Deep Brain Stimulation; SAM, S-adenosylmethionine; SSRIs, Selective Serotonin Reuptake Inhibitors (reviewed in Krajewski *et al.*, 2024).



Life expectancy

In summary due to the observable variable effect on clinical symptoms in LND long-term improvement in the quality of life of these patients needs to outweigh the risk of going through different pharmacological or surgical treatment (DBS). More studies are necessary to better understand the mechanisms that play a role in the disease in order to offer promising prospects for the future of LND treatment. Life expectancy is a difficult issue to address as the extent of the associated clinical conditions of LND has not yet been fully characterized. Fortunately, due to the use of allopurinol, which acts as a substrate for xanthine oxidase, patients with this disorder should no longer die of renal complications. There is a suggestion that some patients may die suddenly in their twenties and thirties possibly because of an unexplained neurological event. Certainly, as the accompanying clinical conditions are managed a longer life expectancy can be anticipated.

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(Prepared by Flora Tassone, June 2025)

Lowe Syndrome

First description and alternative names

Lowe syndrome was first described in 1952 by Dr. Charles Lowe (Lowe *et al.*, 1952). Other names for Lowe Syndrome include cerebrooculorenal syndrome, Lowe oculocerebrorenal syndrome, oculocerebrorenal syndrome, oculocerebrorenal syndrome of Lowe, phosphatidylinositol-4,5-bisphosphate-5-phosphatase deficiency, and OCRL1 syndrome. Lowe syndrome is often referred to medically as oculocerebrorenal syndrome because of the three main organ systems involved (eyes, brain, and kidneys).

Genetics

Lowe syndrome is caused by a mutation or alteration to the OCRL gene on the X chromosome. This gene is responsible for coding an enzyme that helps to regulate the production of certain cells, of which seem to impact primarily the retina, brain, and kidneys (Bökenkamp & Ludwig, 2016; Loi, 2006). The exact mechanism that leads to these three organ systems being primarily affected is not yet known. The OCRL gene has been found to highly expressed in the human hypothalamus, pituitary and other endocrine tissues, areas known to play a role in growth regulation. It is suspected that absence of this gene contributes to the short stature seen in LS and that this may be amenable to growth hormone therapy in future treatment developments (Sena *et al.*, 2022).

A diagnosis of Lowe syndrome is most often confirmed through an enzyme deficiency analysis, usually done by taking a small skin sample. It can also be diagnosed clinically and through DNA analysis (Lewis, 2001). Diagnosis can occur before or after birth. Female carriers of the gene causing Lowe syndrome can be tested, as they usually show changes in the lens of their eye from the age of 10, which can be identified by an ophthalmologist (Röschinger *et al.*, 2000). Carrier status can also be identified through DNA analysis and family history.

Differential Diagnosis

Generalized congenital infections, such as Rubella, are associated with a combination of congenital neonatal-onset cataracts, hypotonia, and kidney dysfunction and should also be considered as a differential diagnosis. There are also a number of different rare genetic conditions that affect similar organ systems to Lowe syndrome, resulting in overlapping symptomology. Overlapping and distinguishing features of other genetic conditions can be found on Gene Reviews (Lewis, 2001).

Prevalence

Lowe syndrome is a rare genetic condition with an estimated prevalence of 1 in 500,000 individuals (Bökenkamp & Ludwig, 2016). It is believed to occur worldwide. Because the condition is X-linked, it primarily affects males. As females have two X chromosomes, it is extremely rare for girls to have Lowe syndrome because both copies of the X chromosome would need to be affected.

Clinical and Physical Phenotype

Vision

Cataracts are present at birth in nearly all cases of Lowe syndrome (Sena *et al.*, 2022). In addition, infantile glaucoma occurs in approximately half of individuals with Lowe syndrome, where there is too much pressure in the eye, causing eyes to become enlarged or appear bulging (Kruger *et al.*, 2003; Loi, 2006; McSpadden, 2000).

Kidney Function

Affected males have varying degrees of proximal renal tubular dysfunction of the renal Fanconi type. In a survey of clinical symptoms by the Lowe Syndrome society, 55.4% of individuals were reported to have kidney calcification, and 21.9% to have renal stones (Sena *et al.*, 2022). Progressive renal tubular injury is thought to eventually lead to chronic kidney disease and end-stage renal disease for many individuals between the second and fourth decades of life.

Facial Characteristics

Elongation of the face is sometimes a feature of Lowe syndrome. Prominent forehead, deep-set eyes, high-arched palate, and fair complexion are also common.

Oral Health

Dental problems are common in LS and are reported by approximately half of parents (Sena *et al.*, 2022). There is often a delayed eruption of adult teeth and overcrowding in the mouth. Teeth will often have white spots due to thin enamel and excessive calcium deposits (Harrison *et al.*, 2000). Cysts can appear in the mouth and gums, leading to infection. Despite the high prevalence of dental problems reported in LS, parents report difficulties accessing dental appointments and supporting dental hygiene at home (Lowenstein *et al.*, 2023).

Musculoskeletal

Hypotonia is present after birth (weak muscle tone), which can cause difficulties with feeding and obtaining motor milestones. Seventy-five percent of boys with Lowe syndrome are able to walk independently between the ages of 6 to 13 years old (McSpadden, 2000). Around 28.5%-50% of individuals with Lowe syndrome develop scoliosis (McSpadden, 2000; Sena *et al.*, 2022). Rickets is common in Lowe syndrome and can often lead to bowing of the legs; however, this can often be prevented with medical treatment. Most individuals with Lowe syndrome will usually have a short stature and fall below the 10th percentile for height (Sena *et al.*, 2022).

Low phosphorus levels may occur in approximately 41.6% of individuals, low vitamin D in approximately 70.2%, with frequency of bone fractures reported to be common at approximately 46% of individuals (Sena *et al.*, 2022).

Puberty

Puberty is often delayed in onset, and between 33-47% of males may experience cryptorchidism (undescended testes; Recker *et al.*, 2014; Sena *et al.*, 2022).

Other

Cysts can often appear in the mouth and skin, such as in the gums, buttocks, and low back, which can cause pain and are at risk of infection (Ikehara & Utani, 2016). Seizures occur in approximately 45- 50% of individuals with Lowe syndrome. There is no specific seizure type (Erdogan *et al.*, 2007; Sena *et al.*, 2022).

Development and Cognition

Although most people with Lowe syndrome will eventually be able to walk, difficulties with motor skills often persist, leading to challenges with tasks such as opening doors, using buttons, shoelaces, zips, keyboards, or pens. Dressing and self-care tasks that require coordination can be particularly difficult. Most individuals will require support in adulthood for tasks such as meal preparation (Sena *et al.*, 2022) and will require support from physical therapy and occupational therapy.

Delayed language is evident in early childhood, but most individuals with Lowe syndrome can imitate words by the age of 2 and a half and can talk by the age of 7 (McSpadden, 2000). Most children with Lowe syndrome become toilet trained between the ages of 5 and 13, although this can be challenging due to constipation, which is thought to affect approximately 70% of individuals (Sena *et al.*, 2022).

Almost all affected males have some degree of intellectual disability, with approximately 10-25% in the low to normal range (borderline), 25% in the mild to moderate range, and 50-65% in the severe to profound range of intellectual disability (Kenworthy *et al.*, 1993).

Behavioural Aspects

Currently, there is little research regarding the social characteristics of individuals with Lowe syndrome. However, parents often report that their children enjoy social interaction but have difficulties interpreting social cues and knowing how to respond appropriately.

Research on parent reports of autistic traits found that 7 out of 10 parents reported that their child had autistic traits, and 3 out of 10 had a score suggestive of an autism diagnosis (Oliver *et al.*, 2010). With regard to formal diagnosis, autism diagnosis has been reported

in approximately 10% of individuals, and Attention Deficit Hyperactivity Disorder in 8.2% of individuals.

Repetitive behaviour is commonly reported in Lowe syndrome (Sena *et al.*, 2022). In a study comparing the prevalence of parent-reported repetitive behaviours across different rare genetic syndromes, hand stereotypies and lining up behaviours were found to be higher in Lowe syndrome compared to other groups (Moss *et al.*, 2008). Hand stereotypy has been noted in approximately 60% of individuals, on survey-based measures (Sena *et al.*, 2022).

Emotional outbursts have been identified as common in Lowe syndrome, with aggression often being a core feature, including behaviours such as self-injury and destruction of property (Cressey *et al.*, 2019; Sena *et al.*, 2022). The most commonly reported triggers are changes in routine and unmet desires (e.g., wanting something that is not available) (Cressey *et al.*, 2019). Some of these difficulties might be related to impaired cognitive processes such as emotional regulation and executive functioning, as similar links have been found in individuals with other rare genetic conditions (Chung *et al.*, 2022; Rice, Woodcock, and Einfeld, 2018). Preliminary research at the University of Birmingham has found that individuals with Lowe syndrome often have difficulties delaying gratification, supporting that executive dysfunction within emotionally salient contexts likely plays an important role in reported emotional regulation difficulties (Waite *et al.*, 2016).

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Ruth Roberts, Jess Hughes and Dr Jane Waite -
Aston University - July 2023

Mowat-Wilson Syndrome

First description and alternative names

Mowat *et al.* (1998) first delineated the syndrome and suggested it was caused by a microdeletion in chromosome 2q22-2q23 or by a de novo mutation of a gene within this region. In 2001, Cacheux *et al.* (2001) and Wakamatsu *et al.* (2001) independently identified the cause of the syndrome to be deletions or intragenic mutations of the ZEB2 gene. Zweier *et al.* (2002) later proposed the name “Mowat-Wilson syndrome”, abbreviated to MWS.

Incidence/prevalence

MWS has an estimated prevalence of 1 in 50,000 – 70,000 live births (Mowat; Wilson, 2010), though several authors suggest it may be more common than originally thought (Adam *et al.*, 2006; Engenheiro *et al.*, 2008; Garavelli, Cerruti-Mainardi, 2007; Mowat, Wilson, & Goossens, 2003). While early publications reported more males than females due to the ascertainment bias of hypospadias and Hirschsprung disease (HSCR), more recent reports suggest MWS affects both genders equally (Garavelli & Cerruti-Mainardi, 2007; Zweier *et al.*, 2005).

Genetics

Mowat-Wilson syndrome is caused by mutation or deletion of the ZEB2 gene, previously known as the Zinc Finger Homeobox 1 B gene (ZFHX1B) located on chromosome 2 at the location 2q22 (Cacheux *et al.*, 2001; Mowat *et al.*, 2003; Wakamatsu *et al.*, 2001). Over 110 different mutations have been reported (Dastot-Le Moal *et al.*, 2007), the majority of which result in premature stop codons. However, in recent years, cases with a milder phenotype resulting from missense mutations and partial loss of ZEB2 function have been reported (Ghoumid *et al.*, 2013; Yoneda *et al.*, 2002; Zweier, Horn, Kraus, Rauch, 2006).

While most cases of MWS occur de novo, germline mosaicism is possible and the recurrence rate is estimated at around 2.3% (Cecconi *et al.*, 2008).

Physical features and natural history

Mowat-Wilson syndrome is characterised by a distinct constellation of facial features in association with variable congenital anomalies. Medical complications can include seizures (in around 80% of cases), Hirschsprung disease (40-50%), severe constipation in those without Hirschsprung disease, agenesis of the corpus callosum (around 45% of cases), congenital heart defects (around 50%), kidney and urogenital anomalies (around 50%). Microcephaly occurs in over 80% of cases (Garavelli & Cerruti-Mainardi, 2007; Mowat; Wilson, 2010). Structural eye anomalies and strabismus have been noted in some people with MWS (Mowat; Wilson 2010), and one case of MWS with bilateral sensorineural hearing loss has been reported (Abdalla, Zayed, 2013).

The facial characteristics of Mowat-Wilson syndrome change with age (Garavelli *et al.*, 2009). Babies generally have a square face with a prominent, triangular-shaped chin, and a broad, saddle nose. With age, the face lengthens, and adults with MWS have a very long chin, with prognathism. By adulthood, the nose has lengthened, has a convex profile and overhangs the philtrum. MWS specific information and growth charts are now available from: <https://mowat-wilson.org/new-diagnosis/welcome-package/> and <https://mowat-wilson.org/2020/10/27/mowat-wilson-syndrome-growth-charts/>.

Other facial features include:

- Hypertelorism (wide set eyes)
- Deep set but large eyes
- Open mouth
- M shaped upper lip
- High arched palate
- Full or everted lower lip
- Fine, sparse hair
- Large uplifted ear lobes with a central depression – arguably the most recognisable feature of MWS. The uplifted lobes remain with age but the depression becomes less marked.
- Flat feet and long, tapering fingers and toes are common, as is short stature.

Behavioural characteristics

A recent study (Evans *et al.*, 2012) reported that the behaviors associated with MWS include a very high rate of oral behaviors (in particular, chewing or mouthing objects or body parts and grinding teeth), an increased rate of repetitive behaviors (such as switching lights on and off; flicking, tapping or twirling objects), and an under-reaction to pain. Other aspects of the MWS behavioral phenotype are suggestive of a happy affect and sociable demeanour. Despite this, those with MWS displayed similarly high levels of behavioral problems as a control group with a similar level of intellectual disability from other causes, with over 30% showing clinically significant levels of behavioral or emotional disturbance.

There are some reports of sleep disturbance in people with MWS (Evans, 2009).

Neuropsychological characteristics

Most people with MWS show a severe-profound level of intellectual disability (ID). However, as the syndrome was identified relatively recently, it is possible that more cases with milder phenotypes will be identified in the future. Motor skills are typically very delayed. While in many individuals, speech is absent or limited to a few words, some have greater success with signing or augmented and alternative communication systems (Evans, 2009). A study found that receptive language was superior to expressive on two measures of communication skills, though the difference in terms of age equivalents was only a few months (Evans, 2009).

Useful websites/associations for more information

- Website and international registry for families affected by MWS:
www.mowatwilson.org
- Australian 'Mowilsi' site:
<http://www.mowatwilsonsupport.org/>
- French forum for families:
<http://smwf.forumactif.org/>
- UK Support group:
<http://www.mowatwilsonsyndrome.org.uk/>
- Italian support group:
<http://www.mowatwilson.it/>

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Neurofibromatosis Type 1 (NF1)

Genetics

Autosomal dominant. Gene localised to 17q11.2. The gene product (neurofibromin) regulates the RAS-MAPK signaling pathway and is thought to suppress tumour formation by regulating cell division (Tidyman, 2009). A high spontaneous mutation rate means that about half of all cases arise in unaffected families.

Incidence/prevalence

About 1 in 2,700 births.

Diagnosis

In those people who do not have a parent with NF1, two of the following must be present to meet diagnostic criteria: (a) 6 or more café au lait macules (>5mm pre-pubertal, >15 mm post-pubertal), (b) axillary or inguinal freckling, (c) two or more neurofibromas of any type, or one plexiform neurofibroma, (d) optic pathway glioma, (e) two or more Lisch nodules, or choroidal abnormalities, (f) a distinctive osseous lesion, (g) a heterozygous pathogenic NF1 variant, with a variant allele fraction of 50% in apparently normal tissue.

In those people who have a parent with NF1, diagnostic criteria are met if one or more features above are present (Legius, Messiaen L, *et al* 2021).

Physical features

Physical manifestations of NF1 include café-au-lait spots, which occur in the first few years of life, intertriginous freckling, Lisch nodules (i.e. pigmented iris hamartomas or freckling in the iris), neurofibromas (i.e. benign Schwann cell tumors, divided into four types: (1) focal or diffuse cutaneous, (2) subcutaneous (under the skin), (3) spinal, and (4) nodular or diffuse plexiform neurofibromas, which develop from nerves and extend into surrounding structures, and which can transform into malignant tumours), optic pathway gliomas, and distinctive bone lesions (e.g., short stature or dystrophic scoliosis). Macrocephaly is common (Huijbregts, 2011).

Life expectancy

For most people with NF1 life expectancy is normal. However, the nature and severity of clinical features may change prognosis.

Brain abnormalities

Magnetic Resonance Imaging studies revealed many different abnormalities in the brains of NF1-patients. These include T2-hyperintensities (of which the nature is not yet known, and which do not seem to have clinical implications), volumetric abnormalities (mainly enlargements of subcortical structures), white matter abnormalities and differences in functional connectivity. The last three appear to be related to cognitive and social outcomes. The lifetime prevalence of epilepsy is reported to be 5.4%. (Bernando, 2020).

Behavioural characteristics

Many patients experience social and behavioural difficulties (Barton & North, 2004). These include communication difficulties and difficulties forming and maintaining friendships. Approximately 25% of children with NF1 meet the diagnostic criteria for autism, and another 25-30% exhibit the broader autistic phenotype (Chisholm, 2022). There is emerging evidence that the autism phenotype in NF1 is more homogenous than idiopathic autism, with reduced restrictive and repetitive behaviours compared to socio-communication difficulties. Cognitive deficits partly underlie the social dysfunction observed in NF1 (Huijbregts & De Sonnevle, 2011). ADHD has been reported in 40—50% (Payne, 2021).

Cognitive characteristics

The global intellectual abilities of individuals with NF1 fall within a normal distribution, albeit towards the lower end of this distribution. More than half of children with NF1 show significant scholastic difficulties. Specific cognitive deficits occur in up to 80% of people with NF1, with attention, executive function and visual perception particularly affected.

Treatment

People with NF1 should be reviewed at least annually and usually require multi-disciplinary care. Monitoring skin and bone changes (scoliosis) are important. Because of the multi-faceted nature of NF1, treatment is generally aimed at specific symptoms. For example, optic glioma are most often treated with chemotherapy (Ardern-Holmes & North, 2011). Also, trials have been performed with bisphosphonate drugs to treat bone abnormalities (Heervä *et al.*, 2014), whilst results of studies using statins to treat social and cognitive impairments were inconclusive at best (Payne *et al.*, 2016; Stivaros *et al.*, 2018; Van der Vaart *et al.*, 2013). Anti-seizure medications are used to treat epilepsy. Methylphenidate does seem to ameliorate some of the cognitive symptoms associated with NF1. Trials are currently underway with new medication (Lamotrigine) to improve cognitive and social functioning via increase of interneuron excitability (Omrani *et al.*, 2015). To date, relatively little attention has been given to non-pharmaceutical interventions, whereas those that have been performed seem to have been relatively successful (e.g. Arnold *et al.*, 2016).

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Noonan Syndrome

First description

The first description of Noonan syndrome (NS) dates back to 1883, when a student named Kobylinski reported on a male patient with several phenotypical characteristics. In 1963, paediatric cardiologists Dr. Jacqueline Noonan and Dorothy Ehmke were the first to identify NS as a distinct syndrome in both male and female patients, with congenital heart defects, small stature, typical faces, skeletal malformations and mild developmental delay (Noonan & Ehmke, 1963; Noonan, 1968). John Opitz, one of Dr. Noonan's students, suggested the eponym and confirmed NS as a nosologic entity.

Associated conditions

NS is a genetic multisystem disorder caused by a pathogenic variant in genes encoding for components of the Ras-MAPK signaling pathway. Syndromes with shared pathogenetic mechanisms and clinical overlap with NS include Noonan syndrome with multiple lentigines (NSML; formerly called LEOPARD syndrome), Noonan-like syndrome with loose anagen hair (NSLH; also called Mazzanti syndrome), Noonan syndrome-like disorder (also called CBL syndrome), Cardiofaciocutaneous syndrome (CFC), Costello syndrome (CS), Legius syndrome (LS), and neurofibromatosis type 1 (NF1). These syndromes are part of a larger group of related conditions known as RASopathies (Tartaglia *et al.*, 2011; Tajan *et al.*, 2018).

Genetics and molecular biology

NS is most often inherited in an autosomal dominant manner, although NS also can be inherited in an autosomal recessive manner. In 60% of patients with autosomal dominant NS, the condition is caused by a de novo mutation. In approximately 50% of patients with NS a missense mutation is found in the PTPN11 gene on chromosome 12 (12q24.13). Germline mutations in more than 14 additional genes involved in the RAS-MAPK pathway have been associated with NS. These genes include SOS1 (10-13% of the cases), RAF1 (5-10%), RIT1 (5%), LZTR1, KRAS, NRAS, MRAS, BRAF, CBL, SOS2, RRAS, RASGEF1B, MAP2K1, and MAP2K2.

In about 20% of the patients with a clinical diagnosis of NS, no variation in the abovementioned genes can yet be found (Allanson & Roberts, 2019; Grant *et al.*, 2018; Liao & Mehta, 2019; Motta *et al.*, 2020; Tartaglia *et al.*, 2022; Zenker, 2022).

Incidence/prevalence

The incidence of NS is estimated between 1 in 1000 to 1 in 2500 live births (Roberts *et al.*, 2013).

Physical features and natural history

Key characteristics are 1) short stature, 2) typical facial dysmorphism (wide-spread and down-slanting eyes, drooping eyelids, and low-set, and posteriorly rotated ears with a thickened helix), and 3) congenital heart defects (pulmonary valve stenosis, hypertrophic cardiomyopathy, and atrial septal defects are most common). Some additional features are variable developmental delay, neonatal feeding difficulties, failure to thrive, hematologic and ectodermal anomalies, skeletal anomalies (e.g., chest deformity), lymphatic diseases, cryptorchidism, ocular abnormalities, widely spaced nipples, and a webbed neck. Neurological complications are relatively uncommon in patients with NS, however, conditions such as hydrocephalus and Chiari type I malformations are described. Epilepsy is also slightly more prevalent compared to the general population. Pain is a common complaint in patients with NS and can sometimes be characterised as neuropathic pain (Draaisma *et al.*, 2024; Leoni *et al.*, 2019).

Life expectancy for patients with NS is fairly normal, unless there are major complications of heart disease. Premature delivery is the main source of morbidity.

It should be noted that phenotypical expression is highly variable in NS and physical characteristics are often milder in adulthood than in childhood. The diagnosis is primarily made on clinical grounds, by observation of cardinal features (Allanson & Roberts, 2019; Noonan, 2005). The most widely used scoring system was developed in 1994 and updated and validated in 2010 (Van der Burgt *et al.*, 1994; DYSCERNE-Noonan Syndrome Guideline Development Group, 2010).

Brain structure and function

Research on brain structure and function in patients with NS is still emerging, but current findings suggest increased connectivity in the visual, ventral attention, left frontoparietal, and limbic networks in children with NS compared to typically developing peers. This hyperconnectivity may contribute to impairments in inhibition, attention, and orientation (Bruno *et al.*, 2022). In a separate study examining brain structures, children with NS were found to have smaller volumes in areas of the corpus striatum - specifically the caudate, putamen, and pallidum - when compared to typically developing children. These brain structures are involved in motivation, motor and action planning, decision-making, and reinforcement processes. A smaller corpus striatum is often associated with inattention and hyperactivity, problems which are frequently seen in children with NS (Johnson *et al.*, 2019).

Behavioural characteristics and psychopathology

There is evidence of an increased risk of behavioural problems in children, primarily characterised by social problems (e.g., problems in understanding social situations, articulating and explaining social experiences, problems in connecting with peers), inattention, hyperactivity, impulsivity and problems in emotion regulation (Alferi *et al.*, 2021; Pierpont, 2016; Pierpont *et al.*, 2018). Internalising problems, characteristics of autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) are more prevalent than in the general population (McNeill *et al.*, 2019; Pierpont, 2016). Externalising problems are also reported in children with NS, but they are less common than internalising problems (Alferi *et al.*, 2014; Pierpont, 2016). In adults with NS, there are indications that internalising problems and social distress are more common (Pierpont 2016; Wingbermühle *et al.*, 2012a, 2022). Higher levels of introversion and alexithymia (i.e., difficulty identifying and verbalising one's own emotions) in adults with NS may contribute to this internalising symptomatology (Roelofs *et al.*, 2019; Wingbermühle *et al.*, 2022).

Neuropsychological characteristics

Intelligence scores show a wide range, with a mildly lowered average intelligence. Intellectual disability (IQ < 70) is present in less than a quarter of patients with NS. No specific or consistent cognitive impairments are found in patients with NS at the group level, when general intelligence or educational level are taken into account (Naylor *et al.*, 2023; Wingbermühle *et al.*, 2022). However, cognitive weaknesses have been identified in various studies. In children, language and motor development are frequently delayed. Research has identified a highly variable cognitive profile in children with NS, with evidence of weaknesses in visual processing, language development, working memory, attention, and planning and organisational skills. These cognitive weaknesses likely contribute to learning problems, which are frequently reported in children with NS, and the need for special education in a number of cases (Kramer *et al.*, 2025; Pierpont 2016). While cognitive weaknesses are frequent in childhood, in adulthood only a lowered speed of information processing and slight problems in emotion recognition are described, although patients report executive function problems in daily life (Wingbermühle *et al.*, 2012a, 2012b).

Available guidelines for assessment/treatment/management

The specific problems that patients with NS may encounter in daily life appear to result from a complex interaction between genetic, somatic, cognitive, psychological, and environmental factors. Therefore, a multidisciplinary approach and intensive collaboration between clinical geneticists, cardiologists, paediatricians, clinical neuropsychologists, physiotherapists, and speech therapists, among others, is necessary to treat patients with NS as best as possible. Moreover, NS is a lifelong developmental disorder, which poses different challenges in different stages of life. Repeated clinical and neuropsychological assessments are recommended throughout the lifespan, particularly at key developmental stages (e.g., before entering primary school and secondary school, and in the transition to adulthood) and when difficulties arise. Based on these assessments, targeted interventions can be provided, such as individualised

educational accommodations, psychological therapy or psychiatric treatment. The recommended multidisciplinary approach and life-long follow-up may be formalised in centres of expertise for patients with NS and other RASopathies. Specific recommendations for the management of patients with NS at different stages of their lives can be found in the international clinical guidelines on Management of Noonan syndrome from the Noonan Syndrome Guideline Development Group (DYSCERNE, 2010). A revised edition will be published in the near future.

More information

- www.dyscerne.org/dysc/Guidelines For the Noonan Syndrome Clinical Management Guidelines.
- www.ncbi.nlm.nih.gov/omim/163950 For the information on NS in OMIM, an online database of human genes and genetic disorders.
- www.noonansyndrome.org.uk For the Noonan syndrome support group Inc.

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Phelan-McDermid Syndrome – (22q13.3 Deletion Syndrome)

Alternative names

Previously known as 22q13.3 Deletion Syndrome, the condition is now commonly called Phelan-McDermid syndrome (PMS). Some individuals have a pathogenic variant of the gene *SHANK3*, but no detectable deletion in 22q13.3. It should be noted that individuals with ring chromosome 22 commonly have a deletion of the distal part of chromosome 22.

History of the syndrome

Ring chromosome 22 was described as a possible deletion syndrome in 1968 (Weleber, Hecht, & Giblett, 1968), and a description of 'pure' partial monosomy syndrome was published by Watt *et al.* (1985). In 1992, Phelan *et al.* published an article with a detailed description of a case with 22q13 deletion (M. C. Phelan *et al.*, 1992). Two subsequent reports highlighting the role of *SHANK3* in explaining the phenotype of the syndrome were published by Bonaglia *et al.* (2001) and Luciani *et al.* (2003). The main characteristics of the PMS phenotype are described below but diagnosis can only be confirmed by genetic analysis. Previously, it was thought that involvement of *SHANK3* was necessary for diagnosing the syndrome, but a recent article has proposed a nomenclature that specifies PMS as being either PMS-*SHANK3* related or PMS-*SHANK3* unrelated (K. Phelan *et al.*, 2022).

Incidence/prevalence

Figures on prevalence are limited; current estimates are around 1/30 000 live births but the syndrome is probably underdiagnosed. Studies in populations with intellectual disability (ID) have reported prevalence figures of PMS ranging from 0.25-3.33 %, with the highest estimates associated with more severe-profound ID (Schön *et al.*, 2023).

Physical features and natural history

The phenotype and natural history of the syndrome are variable. More than 75% of individuals have neonatal hypotonia which may persist into childhood, and motor abnormalities are common (Frank, 2021; K. Phelan, Rogers, & Boccuto, 2018; Schön *et al.*, 2023).

There may be minor morphological features such as large and fleshy hands, long eyelashes or large and prominent ears. Multiple comorbidities can occur throughout the lifetime. Gastrointestinal problems such as gastroesophageal reflux, cyclic vomiting, constipation or diarrhoea, as well as chewing and swallowing problems and frequent airway infections are common in children (K. Phelan *et al.*, 2018).

Epilepsy, involving different types of seizure, can start at any age (Frank, 2021). One study reports that the life time prevalence of epilepsy may be as high as 60% (de Coo, Jesse, Le, Sala, & Bourgeron, 2023).

Cognitive development, behavioural aspects and psychiatric disorders

PMS is characterised by global developmental delay with moderate to profound ID. Marked speech impairment is present in the majority of cases, and alternative and augmentative communication is recommended (Vogels, Droogmans, Vergaelen, Van Buggenhout, & Swillen, 2021). Autism or autism like behaviour is common and is reported in up to 70-80% of individuals with PMS (van Balkom *et al.*, 2023; Vogels *et al.*, 2021). Bipolar disorder and (periodic) catatonic symptoms seem to be particularly prevalent (Verhoeven, Egger, & de Leeuw, 2020). Autism can be identified by the use of the same instruments in PMS as in idiopathic autism, and similarly ID and level of ID can be identified in PMS by the same assessment methods as in individuals without PMS. (Vogels *et al.*, 2021). Many individuals have disturbed sleep. Reduced response to pain is common, and this poses a risk for somatic issues, such as constipation, ear infections, gastroesophageal reflux or dental problems to be diagnosed late or remain unnoticed (Walinga, Jesse, Alhambra, & Van Buggenhout, 2023). Disturbed heat regulation with a tendency to overheat and decreased perspiration are also frequently reported (Frank, 2021).

Regression

Neurodevelopmental regression, with of loss previously acquired skills, is a key feature of PMS (Dille, Lagae, Swillen, & Buggenhout, 2023; Frank, 2021; Reiersen *et al.*, 2017). Regression may involve loss of language/communication, motor or adaptive skills. Both sudden and gradual onset of regression at different ages have been reported. There is no apparent cause in most cases, but symptoms may appear after acute events such as infections, prolonged seizures, or environmental changes. Acute onset of psychiatric symptoms such as catatonia, hallucinations and bipolar disorders can occur in adults. Dille *et al.* (2023) identified a distinct pattern of developmental regression with four stages across the lifespan: (I) Acute onset of language regression in children, (II) followed by a plateau, (III) severe acute-onset psychiatric symptom in adults/adolescents and (IV) late neuromotor deterioration. The last stage is often preceded by an acute trigger or event such as severe sickness, hormonal shifts, and psychosocial stress. Diagnostic identification and appropriate treatment of psychiatric and somatic disorders are essential when regression occurs.

Genotype Phenotype correlations

SHANK3 is considered the major gene for PMS, and this gene is closely linked to autism symptoms. In general, a smaller deletion is associated with higher cognitive and adaptive levels. Previously, it had been thought that the clinical features were apparent in all individuals with a non-mosaic 22q13.3 deletion, but it has been reported that small deletions of *SHANK3* may have variable penetrance suggesting that some individuals may have compensating mechanisms (Tabet *et al.*, 2017). It should be noted that some individuals seem to have additional copy number variations (CNVs) such as 16p11.2 and 15q11q13 contributing to the phenotype (Tabet *et al.*, 2017). Neurofibromatosis type 2 (NF2) pathogenic variants lie adjacent to the region deleted in PMS, and individuals with ring chromosome 22 have a specific risk of developing (NF2). These individuals should be followed as if they had an affected parent (K. Phelan *et al.*, 2018).

Available guidelines

European Journal of Medical Genetics have published European consensus guidelines for PMS, which were supported by The European Reference Network ITHACA (Intellectual disability, TeleHealth, Autism and Congenital Anomalies) (van Ravenswaaij-Arts *et al* 2023).

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Kristin A Bakke and Sissel Berge Helverschou : June 2023

Prader-Willi Syndrome (PWS)

First description

Prader-Willi syndrome (PWS) was first described in 1956 by Prader, Labhart and Willi. It was known as H³O syndrome because of the characteristic symptoms of hypotonia, hypogonadism, hyperphagia and obesity.

Genetics and molecular biology

PWS results from the absence of expression of the paternal allele of paternally expressed/maternally imprinted genes at the chromosomal locus 15q11-q13 (the PWS critical region). The commonest genetic mechanisms leading to PWS are: a) a de novo deletion at the PWS critical region on the chromosome of paternal origin (60%) and b) maternal uniparental disomy (mUPD) of chromosome 15 where both chromosomes are derived from the mother (36%) (Butler *et al.* 2019). Other rarer causes of PWS include imprinting centre defects (4%) and unbalanced translocations. A number of paternally expressed/maternally imprinted genes have been identified within the PWSCR of which the largest is *SNRPN* (containing the imprinting centre) which codes for a small nuclear ribosomal protein involved in the control of synthesis of proteins related to hypothalamic function. Imprinted and non-imprinted genes are found within the deleted region; *SNORD 116*, *MAGEL 2* and *NECDIN* being the genes whose absence of expression at the locus 15q11-13 are considered central to PWS. Knock-out mouse models and studies of people with mutations in the *MAGEL2* (i.e. Schaaf-Yang syndrome) and/or *NECDIN* genes suggest that these genes are involved in hypotonia, respiratory problems, sleep abnormalities, adiposity, developmental and cognitive delay, socialisation difficulties and skin picking (Fountain *et al.* 2017a, 2017b; Matarazzo *et al.* 2017; Muscatelli *et al.* 2000). However, two people have been described lacking expression of the genes *MKRN3*, *MAGEL2* and *NECDIN* but showing only developmental and cognitive delay from the major PWS criteria (see Holm *et al.* 1993 for consensus diagnostic criteria) and a high pain threshold from minor criteria (Kanber *et al.* 2009; Buiting *et al.* 2014). Also, accounts in the literature of people with very

small deletions, not involving *MKRN3*, *MAGEL2* or *NECDIN*, but with most or all PWS characteristics also support the non-involvement of these genes in the PWS core characteristics in humans (Sahoo *et al.* 2008; de Smith *et al.* 2009; Duker *et al.* 2010). Core characteristics in these cases were: hypotonia, early feeding difficulties, hyperphagia/obesity, hypogonadism, intellectual disability and behaviour problems. The most likely single candidate gene, from studies of people with PWS, is now considered to be the imprinted gene *SNORD116*. *SNORD116* changes the expression levels of multiple genes (Falaleeva *et al.* 2015), which may explain why, in PWS, it is able to affect so many systems.

In developed countries, diagnosis is usually made clinically based on severe hypotonia at birth, and followed by genetic testing. Mahmoud *et al.* (2019) carried out a feasibility study which showed that newborn screening was accurate, able to differentiate genetic subtypes, and could lead to earlier intervention with better outcomes.

Incidence/prevalence

The estimated birth incidence is 1 in 25,000 (Whittington *et al.*, 2001; Vogels *et al.*, 2003; Smith *et al.*, 2003; Diene *et al.*, 2010). Prevalence will vary across populations and time according to the death rates: the higher the death rate, the lower the prevalence.

Natural history

The early phenotype is characterised by severe hypotonia after birth, which affects the infant's ability to suck, resulting in feeding problems and consequent failure to thrive which may necessitate gavage feeding. Hypothalamic dysfunction leading to growth hormone and steroidal sex hormone deficiency may account for several features of PWS (Goldstone 2004), including the control of birth processes, short stature, hypogonadism, aberrant body temperature control and daytime hypersomnolence. Characteristic facial features include dolichocephaly, narrow bifrontal

diameter, almond shaped palpebral fissures, small down turned mouth and thin upper lip (Holm *et al.* 1993).

The onset of the striking characteristic of hyperphagia separates the early and late phenotype. Between the ages of 1 and 6 years, the child develops a propensity for eating which, if left unaddressed, can result in obesity and medical problems. The hyperphagia is considered to be hypothalamic in origin, and caused by failure of the normal satiety response following food intake (Holland *et al.* 1993; Hinton *et al.* 2005). Infertility remains almost universally present although there are rare reports of children being born to females with PWS.

Behavioural and psychiatric characteristics

The main behavioural techniques used to address hyperphagia include preventing access to food e.g. by locking cupboards, low calorie diets, all members of the household having the same diet and ongoing education about the risks of overeating. Appetite suppressants and gastric banding have not been shown to be useful. Octreotide has been shown to decrease concentrations of ghrelin in adolescents with PWS, but does not reduce appetite or BMI (De Waele *et al.* 2008). This year the drug Vykat XR has been approved in the USA (2025) for treatment of hyperphagia in PWS.

Aside from the over-eating, the most common problem behaviours are temper tantrums, mood swings which do not fulfil criteria for a defined psychiatric disorder; ritualistic and repetitive behaviours; and self-mutilation in the form of skin-picking. Evidence suggests that modulation of the glutaminergic pathway may reduce the compulsive behaviours; oral N-acetylcysteine was found to reduce skin picking, although participants with PWS were not compared with a control group (Miller & Angulo 2013). A small study of vagus nerve stimulation found great improvement of problem behaviours, although not hyperphagia (Manning *et al.* 2016).

A comprehensive study of 101 participants with PWS found that temper outbursts decreased in frequency with age, while the duration of outbursts increased. Provocations fitted in to three themes: goal blockage, social injustice, and difficulty dealing with change.

Medications were prescribed, but were not found to be particularly effective (Rice *et al.* 2018). Temper outbursts are associated with task switching and can be reduced by signalling in advance that a change is coming (Bull *et al.* 2017).

Relative to others with intellectual disability, people with PWS are more likely to exhibit severe problem behaviours (Dykens *et al.* 1997). Obsessional traits occur commonly, in particular needing to ask or tell, requiring routines, hoarding and repetitive questioning (Clarke *et al.* 2002). It has been found that people with PWS who are exposed to routines for longer before a change are more likely to engage in temper outburst behaviours (Bull *et al.* 2014).

The mUPD genetic subtype of PWS is strongly associated with the development of affective psychosis (Boer *et al.* 2002). In a UK-wide sample of 119 adults with PWS, 62% of those with mUPD had a diagnosis of psychotic illness compared with 17% of those with a deletion (Soni *et al.* 2008). Atypical symptoms such as hypersomnia and confusion were seen, and those with mUPD had a more severe, difficult-to-treat illness with a poorer outcome compared to those with a deletion (Soni *et al.* 2007). However, once stability has been achieved in psychotic illness, recurrence rates are low (Larson *et al.* 2013). Dementias are now being documented as individuals survive into old age (Sinnema *et al.* 2010). Autism has been reported (Veltman *et al.* 2004); candidate genes for autism have been located within the 15q11-q13 region and there is evidence that those with mUPD may be more severely affected than those with a deletion (Ogata *et al.* 2014).

A review of the literature in order to understand how best to conceptualise behaviours and abnormal mood states associated with PWS was undertaken by Whittington & Holland (2018). Many behaviours such as eating behaviour, obsessive compulsive behaviours and skin picking, appear to have a strong genetic aetiology, whereas depression and psychosis have both genetic and environmental aetiological components. The authors caution against using standardised diagnostic labels to describe common PWS behaviours (e.g. repetitive ritualistic behaviours typical in PWS are not equivalent to those seen in OCD) as this may lead to inappropriate treatments.

Neuropsychological characteristics

The full scale IQ is usually in the mild intellectual disability range, and a mean downward shift of approximately 40 points compared to the general population is seen (Whittington *et al.* 2004). Those with mUPD tend to have better verbal skills and those with a deletion have better visuo-spatial skills. Also seen are poor short-term memory, deficits in sequential processing, poor socialisation skills, deficits in comprehension, abstract reasoning, recognising emotions and appreciating the concept of time. (See Whittington & Holland (2018) for a review of cognition in PWS).

Neuroimaging findings

Functional and anatomical studies have implicated a combination of subcortical and higher order structures in PWS, including those involved in processing reward, motivation, affect and higher order cognitive functions (Manning & Holland 2015).

It is generally accepted that the root of many PWS characteristics lies in the hypothalamus and recently it has been shown that the hypothalamus in PWS is small compared to typical development (Brown *et al.* 2022).

A study by Lukoshe *et al.* (2013) looked at high resolution structural magnetic resonance imaging in children with confirmed PWS. All children with PWS showed signs of impaired brain growth. Those with mUPD showed signs of early brain atrophy. In contrast, children with a deletion showed signs of fundamentally arrested, although not deviant, brain development and presented few signs of cortical atrophy. The authors suggest that there are divergent neurodevelopmental patterns in children with a deletion versus those with mUPD.

Increased brain age was seen in adults with PWS who underwent MRI scanning (Azor *et al.* 2019). This was independent of high BMI, or use of growth and sex hormones, and may reflect premature brain aging or abnormal brain development.

Physical health and endocrine

The most prevalent physical health problems in people with PWS are scoliosis, respiratory problems, dermatological lesions, hyperlipidaemia, hypothyroidism, Type 2 diabetes mellitus and lymphoedema (Laurier *et al.* 2014).

Growth hormone supplementation can increase height and the rate of growth, decrease mean body fat, improve respiratory muscle function and physical strength and improve facial dysmorphism. However, after cessation of growth hormone therapy, BMI can increase again, and long term therapy may be indicated (Oto *et al.* 2014). Furthermore, cessation of growth hormone therapy may lead to successive deterioration in behaviours in children with PWS (Bohm *et al.* 2014).

In 2021, the International Prader-Willi Organisation called for approval of Growth Hormone Replacement Therapy (GHt), not only in children with PWS but also extending throughout the lifespan (Hoybye *et al.*). They noted that GHt was already fairly widely approved for children with PWS, beginning with the USA and EU in the 1990s. Although effects on height and early motor development were absent for obvious reasons, the benefits reported in the literature in adults with PWS were otherwise similar to those observed in children with the syndrome. In summary these are: normalisation of IGF-I levels, increase in lean body mass, decrease in body fat, improved physical fitness, and beneficial effects on cardiovascular risk markers, and on behaviour and quality of life. The authors also touched on the two contra-indications: serious sleep apnoea and untreatable diabetes mellitus, cautioning that sleep studies should be carried out before GHt can be prescribed and that GHt should not be used in people with untreatable diabetes mellitus.

A study by Cohen *et al.* (2014) showed that central sleep apnea with associated oxygen desaturations is more prevalent in infants compared with older children with PWS. The authors found that supplemental oxygen was efficacious in treating central sleep apnea in infants and advised routine sleep surveillance for all children with PWS with consideration given to oxygen therapy.

Symptoms of constipation are common in people with PWS with up to 40% fulfilling defined criteria

for constipation in a study by Kuhlmann *et al.* 2014. These symptoms cannot be explained by abnormal eating habits. Gastrointestinal transit times are also increased compared with the general population and may in part be related to poor muscle tone. Studies have shown that people with PWS produce less saliva and have a high risk of choking. A pilot study by Gross *et al.* (2014) showed that food was visualised on x-ray, lodged in throats, but the people with PWS were unaware of it.

Osteoporosis, osteopenia and fractures are relatively common in people with PWS. Growth hormone treatment can improve bone size and strength but not bone mineral density in people with PWS (Longhi *et al.* 2015).

Useful websites/associations for more information

- PWS Association UK:
www.pwsa.co.uk
- PWS Association USA:
www.pwsausa.org
- IPWSO (International PWS Organisation):
www.ipwso.org
- Online Mendelian Inheritance in Man (OMIM):
www.omim.org

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Updated May 2025: Joyce Whittington

Rubinstein-Taybi Syndrome (RTS)

Prevalence

Although prevalence estimates have varied it is thought that the most accurate estimate is approximately 1 in 100,000 to 125,000 live births.

Genetics

Genetic markers are found in around 65-70% of cases and some individuals are diagnosed through clinical characteristics alone. RTS can be divided into two types: RTS1 and RTS2. These types are linked to heterozygous pathogenic changes or re-arrangements in the genes CREBBP and EP300, respectively. Both CREBBP and EP300 genes encode paralogous transcriptional coactivators with Lysine Acetyl Transferase Activity. CBP and p300 proteins are vital in initiating transcription. There are only a small number of reports of the clinical and behavioural features of RTS2, and these reports have indicated individuals are often more mildly affected, particularly in terms of the skeletal features and degree of intellectual disability.

Physical features

The physical characteristics associated with RTS have been well documented and include broad thumbs and toes, microcephaly, excessive hair growth and dental abnormalities (including narrow high-arched palate). The classical facial appearance changes with age. Descriptions in adults typically include low hanging columella, eyes with downward slanting palpebral fissures, long eyelashes, thick eyebrows, and a small mouth. Feeding problems are often present at birth, with descriptions of poor appetite, vomiting and failure to thrive during infancy, followed by enhanced appetite and weight gain in adolescence. Other health problems include renal abnormalities, constipation, recurrent upper respiratory infections, undescended testes in males and keloids.

Behavioural characteristics

Although still in its infancy, the literature outlining the behavioural phenotype of RTS is growing. In 2022, the literature was reviewed systematically, to describe the patterns of behaviour in RTS. The

two most frequently noted characteristics relate to social behaviour and repetitive behaviour. Reports have described those with RTS as “overfriendly” and “happy” individuals who “love adult attention” and “know no strangers”. Such descriptions have led to the suggestion that individuals with RTS may show some enhanced, or preserved, social communication skills when compared to those with other causes of ID. Stereotyped behaviours such as rocking, spinning, and hand flapping, appear to be common. Other repetitive behaviours noted in around three quarters of individuals with RTS include an adherence to routine and an insistence on sameness.

Studies have also described sleeping difficulties, a tendency for individuals to be “emotional” and “excitable”, and “stubbornness”. The presence of ADHD-type behaviour, such as impulsivity and hyperactivity, has also been noted. Studies have commented on challenging behaviour in individuals with RTS, including aggressive behaviours and self-injurious behaviours, although evidence that these are more common in RTS than in ID generally is lacking.

Emotional Characteristics

Despite some studies showing social competency and social skills, other research has indicated that individuals with RTS demonstrate higher levels of social anxiety than those with Down syndrome across a range of social situations with both familiar and unfamiliar adults. Adolescents with RTS have been shown to be more likely to exhibit greater anxiety symptoms than infants and children with RTS. It has also been suggested that individuals with RTS may be at increased risk of mood instability and emotional outbursts as they get older. More research is needed to explore the emotional and psychiatric characteristics of individuals with RTS.

Cognitive characteristics

Intellectual disability (ID) is an associated characteristic of RTS. Although estimates regarding the degree of ID have varied across studies, and there is a wide range of IQs within the syndrome, it is thought that

most individuals lie within the moderate range. Genetics studies have started to link the molecular abnormalities to cognitive dysfunction in RTS. The CREB binding protein implicated in RTS has been shown to underlie long term memory formation and consequently it has been suggested that ID may be related to impaired long-term memory. Preliminary work assessing social cognition in RTS indicates some 'precursor' social cognitive abilities are intact but there may be subsequent deficits in later developing Theory of Mind. In addition, there is emerging evidence that executive function abilities may be compromised in RTS relative to mental age and that these difficulties may be related to repetitive behaviours observed in the syndrome.

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Rett Syndrome (RTT)

Rett Syndrome (RTT, OMIM no 312750) is a rare neurological disorder characterized by a broad spectrum of symptoms.

First description

Rett Syndrome (RTT) was first described (in German) by an Austrian neurologist, Dr. Andreas Rett, in 1966, following his observation of the characteristic “hand washing” movements of his patients (Rett, 1966). It was not until the 1980s, however, that the syndrome began to be recognised more widely, as a result of English-language publications written by a Swedish neurologist, Dr. Bengt Hagberg (Hagberg, 1985; Hagberg, Aicardi, Dias, & Ramos, 1983). It was he who proposed the name “Rett syndrome” in recognition of the role played by Andreas Rett in first identifying the disorder.

Genetics

In the majority of individuals with RTT, the cause can be attributed to de novo mutations in the X-linked Methyl-CpGbinding protein 2 gene (*MECP2*) located at Xq28 (Amir *et al.*, 1999). *MECP2* is a transcriptional repressor that binds methylated DNA and influences many different biological pathways on multiple levels (Lyst & Bird, 2015). Phenotype-genotype correlation studies indicate that certain mutations may contribute to higher or lower levels of neurologic function and developmental skills (Fabio *et al.*, 2014; Fehr, Downs, Bebbington, & Leonard, 2010; Leonard *et al.*, 2005; Neul *et al.*, 2014). Other (epigenetic) factors are also playing a role in determining severity, such as X chromosome inactivation and distribution of the abnormal gene in specific brain regions (Cuddapah *et al.*, 2014; Neul *et al.*, 2008). However, mutations in *MECP2* cannot be identified in all cases (or may be detected when no phenotypic characteristics are present) and the primary diagnosis still remains clinical rather than genetic.

FOXP1 and *CDKL5* are known genes, which also cause RTT-like phenotypes. These now fall under a banner of RTT-related disorders. The number of known genes, in which variation can cause a RTT-like phenotype,

increased drastically in the last few years; there have been 69 new genes identified which can cause a RTT (classic or variety) like phenotype (Ehrhart, Sangani, & Curfs, 2018). We are possibly heading towards a RTT spectrum disorder with many causative genes (Ehrhart *et al.*, 2018). How much influence a particular mutation has and how much is contributed by other genetic aspects or environmental influences is an open question (Ehrhart *et al.*, 2021).

Incidence/prevalence

As RTT is an X-linked disorder it is seen predominantly in females, with an estimated prevalence of 1 in 9,000-15,000 live female births (Bienvenu *et al.*, 2006; Fehr *et al.*, 2011), making this one of the most frequent causes of developmental disorder in girls. It is more rarely found in males, in whom early deaths have been reported.

Life expectancy/mortality

Individuals with RTT commonly have a reduced life span compared with the general population (Halbach *et al.*, 2013), with the most physically challenged being at increased risk of early death and the most able surviving into adulthood in good health. There is a high incidence of sudden death, which may be related to central autonomic dysregulation (Kerr, Armstrong, Prescott, Doyle, & Kearney, 1997). Some deaths are related to epilepsy, to aspiration pneumonia or nutritional difficulties but less severely affected individuals are likely to die from causes unrelated to RTT.

Physical features and natural history

Typically, RTT has been characterised by seemingly-normal development in the early months of life following which there is a stagnation and regression of skills, beginning between 6 and 18 months of age (Lee, Leonard, Piek, & Downs, 2013; Smeets, Pelc, & Dan, 2012). Recent retrospective studies have, however, shown that early development does not follow quite as typical a trajectory as supposed (Einspieler, Kerr, & Pechtl, 2005; Marschik *et al.*, 2014; Marschik *et al.*,

2013). Developmental regression in RTT remains still a puzzling and complex phenomena (Einspieler & Marschik, 2019; Smeets, Townend, & Curfs, 2019; Zhang *et al.*, 2019).

One of the first noticeable signs is a deceleration in head growth. Other symptoms include loss of motor and communication skills, namely the loss of verbal language and purposeful hand use, accompanied by stereotypic hand movements (the handwashing/clapping noticed by Andreas Rett). Additional features include abnormal gait and an inability to walk; abnormal breathing and sleep patterns, altered muscle tone, scoliosis, growth retardation and small cold hands and feet (Neul *et al.*, 2010). Poorly regulated central autonomic function leads to disturbed cardio-respiratory control with episodes of breath-holding, shallow breathing, hyperventilation and valsalva breathing. Epilepsy is present in 60%–80% of individuals (Operto, Mazza, Pastorino, Verrotti, & Coppola, 2019). Early hypotonia gives way to hypertonia with the risk of contractures and episodes of dystonia are common. Abnormal oral movements may make feeding difficult. Gastric reflux, aerophagy and constipation are common.

Communicative, cognitive and behavioural characteristics

Anxiety and mood disorders are frequently reported. Perhaps the most significant factor influencing quality of life for individuals with RTT and their families, however, is the severe limitation in their ability to communicate through conventional channels such as speech and hand signs/gestures (Cass *et al.*, 2003). To what extent apraxia rather than any deeper language and cognitive impairments influences these limitations, is a subject for ongoing debate. In general, older studies suggest that most individuals with RTT operate at pre-linguistic, pre-intentional levels of communication. Several studies also point to low levels of language comprehension and cognitive functioning (Berger-Sweeney, 2011), especially when standardised receptive language, IQ or adaptive behaviour tests are employed. In contrast, parents frequently report that their children know more than they are able to express or to demonstrate on assessment (Bartolotta, Zipp, Simpkins, & Glazewski,

2011; Urbanowicz, Leonard, Girdler, Ciccone, & Downs, 2014) and there is growing (anecdotal) evidence that the population of individuals with RTT spans a broader range of cognitive ability than previous thought. They are universally recognised as engaging in “intense eye communication” (Neul *et al.*, 2010) (p. 946) and many parents and professionals advocate an approach of “presumed competence”. There is growing interest in the potential benefits that eye gaze/eye-tracking technologies can offer to individuals with RTT (Townend *et al.*, 2016). This has led to calls for the development of more objective eye gaze/eye-tracking based cognitive and receptive language assessments, which can be used to validate parental reports (Byiers & Symons, 2013; Urbanowicz *et al.*, 2014)..

Differential diagnosis

Clinical criteria for the diagnosis of classic RTT and its atypical variants e.g. Preserved Speech Variant (Renieri *et al.*, 2009) were revised in 2010 by members of the Rett Search consortium (Neul *et al.*, 2010). Following clinical identification by core and supportive consensus criteria, the diagnosis may be confirmed by genetic analysis.

Historically, individuals with RTT were labelled as having an “autism spectrum disorder” (ASD) (Young *et al.*, 2008), however, RTT was removed from the umbrella of ASD in the 2013 publication of DSM-V. While individuals with RTT pass through an autistic-like phase during regression, many regain social awareness and are especially noted for their sociability. Those with milder atypical forms of RTT (e.g. PSV) may continue to display features of ASD (Kaufmann *et al.*, 2012).

Management

In 2007 Bird and colleagues first demonstrated that the symptoms of RTT could be reversed in mice (Guy, Gan, Selfridge, Cobb, & Bird, 2007). Since then much research has been devoted to both the treatment and potential cure of RTT (although this continues to be quite some way off) as well as the development of more functional therapies which address day to day care and seek to enhance the participation and quality of life of individuals living with this rare disorder.

Due to their complex physical and psychological needs individuals with RTT and their families require

lifelong access to assessment and intervention from expert multidisciplinary teams (Borloz, Villard, & Roux, 2021; Nissanholtz-Gannot, Zigdon, & Lotan, 2015). Parent associations can also play a vital role in supporting families (Townend *et al.*, 2016). Specialist advice is needed in relation to aspects such as feeding and nutritional, epilepsy and non-epileptic autonomic attacks, movement and posture, and communication. Furthermore, fundamental RTT research findings are providing a better understanding of the underlying mechanisms of the disease and paving the road towards therapies (Sandweiss, Brandt, & Zoghbi, 2020).

Available guidelines

In recent years, guidelines have been written for the management of scoliosis (Downs *et al.*, 2009), growth and nutrition (Leonard *et al.*, 2013), and bone health (Jefferson *et al.*, 2016) in RTT. An international consortium with 650 participants from 43 countries led by the Rett Expertise Centre Netherlands-GKC developed consensus based guidelines for the assessment, intervention and long-term management of communication in RTT (Townend, Bartolotta, Urbanowicz, Wandin, & Curfs, 2020).

Conclusion

We do not yet fully understand the biological pathways underlying the phenotypic presentation of the syndrome. Next generation sequencing, especially whole genome sequencing, combined with the use of bioinformatics analysis and mutation databases find more and more genes in patients who were clinically diagnosed with RTT or RTT like syndrome (Ehrhart *et al.*, 2021; Ehrhart *et al.*, 2018). Integrative analysis of omics data and creating a better interoperability between genotype-phenotype databases will increase our power to do so. Further research into the pathophysiology of RTT for a better understanding of the multifunctionality of MECP2 and at the same time offering patients and their families' good clinical care is the way to go.

Useful websites/associations for more information

- <http://www.rettssyndrome.org>
- <http://www.rettssyndrome.eu/association-rse/europe/>

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SATB2-Associated Syndrome

First description and alternative names

Glass *et al.* (1989) first described a male with a 2q32.2-q33.1 deletion that included the *special AT-rich sequence-binding protein 2 (SATB2)* gene, subsequently, the name 'Glass syndrome' (OMIM #612313) was proposed.

Since 1989, varying genetic alternations to the *SATB2* gene have been documented to produce a relatively consistent phenotype, independent of the underlying pathogenic variant. Phenotypic differences are thought to relate to differences in severity rather than the system affected (Zarate & Fish, 2017). *SATB2*-associated syndrome (SAS) was therefore designated as a single clinically recognised syndrome in 2014, in an effort to unify the terms for different alterations affecting the *SATB2* gene (Döcker *et al.*, 2014).

In addition to Glass Syndrome, alternative names include 2q32 Deletion Syndrome, 2q33.1 Microdeletion Syndrome, and Chromosome 2q32-q33 Deletion Syndrome.

Genetics

The SAS phenotype is associated with alterations causing functional haploinsufficiency of the *SATB2* gene (OMIM #608148) located on chromosome 2q33.1 (Cotton *et al.*, 2020; Zarate & Fish, 2017). Alterations can result from a variety of molecular mechanisms, such as missense (31%), nonsense (24%), frameshift (20%), and intragenic deletion (14%) (Zarate *et al.*, 2019).

SAS is an autosomal dominant disorder (an abnormal gene from one parent can cause *SATB2*). For most individuals, SAS is reported to occur as the result of a de novo alteration to the *SATB2* gene; however, instances of mosaicism (where a percentage of cells in the body are affected by the genetic alteration) have been documented (Leoyklang *et al.*, 2007; Zarate *et al.*, 2019).

The *SATB2* gene is a regulator of several gene regulatory networks (GRNs) and has critical roles in multiple developmental processes, including skeletogenesis (skeleton formation), osteogenesis (bone formation) and craniofacial patterning (skull and facial formation) (Britanova *et al.*, 2006; Dobрева *et al.*, 2006; Gong *et al.*, 2014). The *SATB2* gene is also

expressed in the developing cortex and other tissues including the kidney and gut (Alcamo *et al.*, 2008; Britanova *et al.*, 2008). The presence of intellectual disability and speech delay/absence in individuals with SAS has been attributed to the essential role of the *SATB2* gene in neuronal connectivity (Döcker *et al.*, 2014).

Incidence/prevalence

SAS is estimated to occur in approximately .24-.30% of individuals with an undiagnosed intellectual disability or developmental delay (Bengani *et al.*, 2017; Zarate *et al.*, 2018). An incidence rate of approximately 1 in 30,000 births has been reported (López-Rivera *et al.*, 2020).

Physical features and natural history

The core features of SAS have been incorporated into a S.A.T.B.2 acronym; Severe speech anomalies, Abnormalities of the palate, Teeth anomalies, Behavioural difficulties, with or without bone anomalies and/or brain defects, and observable characteristics by 2 years of age (Zarate & Fish, 2017).

Minor facial dysmorphisms have been described in individuals with SAS, including a thin upper lip, flat philtrum (groove between the upper lip and nose), prominent chin, micrognathia (small lower jaw), abnormal dentition, deeply set eyes, low-set ears, and a prominent forehead or high anterior hairline (Zarate & Fish, 2017; Zarate *et al.*, 2017; Zarate *et al.*, 2018). Facial change with age is reported, with progressive coarsening of facial features in older individuals (Zarate *et al.*, 2018).

Craniofacial and dental abnormalities are characteristic of individuals with SAS. Frequently reported palatal abnormalities include cleft palate and high-arched palate, while bifid uvula (split soft palate at the back of the throat) has been reported in a small number of individuals (Zarate *et al.*, 2019). Dental abnormalities are present in all individuals and become apparent from one year of age (Zarate *et al.*, 2018). Delayed development of the mandibular second premolars (premolars on the lower jaw) or roots of the

permanent teeth, dental crowding with malocclusion (misalignment of the upper and lower teeth), abnormal tooth shape, and multiple odontomas (benign tumours linked to tooth development) are reported (Kikuri *et al.*, 2018; Scott *et al.*, 2018; Zarate *et al.*, 2018). Sialorrhea (drooling or excessive salivation) is often present (Zarate *et al.*, 2018).

Feeding difficulties (e.g., choking, overstuffing, and problems chewing) are common during infancy and early childhood and have been attributed to the combination of craniofacial abnormalities and hypotonia (low muscle tone; Zarate *et al.*, 2017; Zarate *et al.*, 2018). Many infants are of low birth weight and low weight often persists. Tube feeding is often required in infancy, and this process may continue for several years (Zarate *et al.*, 2019; Zarate *et al.*, 2018). Gastrointestinal difficulties are reported, including constipation and/or gastro-oesophageal reflux (Zarate *et al.*, 2021; Zarate *et al.*, 2017).

In some individuals with SAS, skeletal abnormalities have been reported, including scoliosis, tibial bowing (bowing shin bone), pectus excavatum (sunken breastbone), and low bone mineralisation density (Mouillé *et al.*, 2022; Zarate *et al.*, 2018). While most individuals are mobile (Bissell *et al.*, 2022), difficulties with movement and balance are reported (Zarate & Fish, 2017; Zarate *et al.*, 2017). Hypotonia is reported in 42-74% of individuals (Zarate & Fish, 2017; Zarate *et al.*, 2018). An average age of 25.5 months has been reported for individuals taking their first steps (Zarate *et al.*, 2019).

Clinical seizures are present in approximately 20% of individuals with SAS (Lewis *et al.*, 2020; Zarate *et al.*, 2018). Subclinical seizures with abnormal electroencephalogram (EEG) activity have also been observed (Zarate & Fish, 2017; Zarate *et al.*, 2017). Abnormal EEG activity has included abnormal wakefulness (staring spells, disorientation episodes, and/or laughing fits), slow background, and/or epileptiform discharges (Lewis *et al.*, 2020; Zarate *et al.*, 2018).

Other health problems include otitis media (middle ear infections), visual problems (e.g., strabismus (squint) and refractive errors), genitourinary problems and cardiac defects (Bissell *et al.*, 2022; Zarate & Fish, 2017; Zarate *et al.*, 2021; Zarate *et al.*, 2017).

Behavioural characteristics

Individuals with SAS often display a happy disposition or friendly demeanour, with heightened motivation for social contact (Zarate *et al.*, 2017; Zarate *et al.*, 2018). However, this may be offset by the presence of behaviour that challenges, which are outlined within the S.A.T.B.2 acronym (Zarate & Fish, 2017; Zarate *et al.*, 2017). High rates of self-injury (43%), property destruction (49%) and aggression (77%) are reported (Shelley *et al.*, 2024). Rates of self-injury and aggression in SAS are comparable to rates in non-syndromic autism and Angelman syndrome, while rates of property destruction are lower in SAS compared with non-syndromic autism and Angelman syndrome (Bissell *et al.*, 2022).

Self-injurious behaviours, aggressive behaviours, and destruction of property behaviours are present in children, adolescents, and adults with SAS (Bissell *et al.*, 2022). Behavioural changes with age are also indicated from clinical observations suggesting temper outbursts in childhood, with more physical acts of aggression emerging in adolescence and adulthood (Zarate *et al.*, 2017).

An association between SAS and autism characteristics has been consistently reported (Lewis *et al.*, 2020; Zarate & Fish, 2017; Zarate *et al.*, 2021; Zarate *et al.*, 2019). Bissell *et al.* (2022) report 46% of individuals met cut-off scores suggestive of autism spectrum disorder (ASD) according to the Social Communication Questionnaire (Berument *et al.*, 1999). This concurs with rates of ASD (46%) reported by Zarate *et al.* (2021). Reported rates of ASD in SAS are comparatively high on screening measures compared to the prevalence of ASD in other syndrome groups associated with autism and intellectual disability (Richards *et al.*, 2015). Fine-grained analyses reveal a distinct profile of autism characteristics and repetitive behaviour in SAS relative to individuals with non-syndromic autism. Key findings include convergent levels of compulsive behaviour and insistence on sameness, and differences in reciprocal social interaction and restrictive, repetitive, and stereotyped behaviour (Bissell *et al.*, 2022). Impulsivity and hyperactivity are also frequently reported as behavioural features of SAS (Bissell *et al.*, 2022; Lewis *et al.*, 2020; Zarate & Fish, 2017; Zarate *et al.*, 2019).

Sleep difficulties are common in children and adults with SAS and are reported to occur in between 50% and 75% of individuals. Difficulties include problems with initiating and maintaining sleep, sleep-wake transitions, early awakening, and sleep-breathing disorders (Cotton *et al.*, 2020; Kumar & Zarate, 2020; Zarate *et al.*, 2021).

Atypical sensory processing has been described in some individuals. This has included reports of hypersensitivity to sound and touch (Balasubramanian *et al.*, 2011; Tomaszewska *et al.*, 2013; Zarate & Fish, 2017) and a high pain-threshold (Rosenfield *et al.*, 2009; Scott *et al.*, 2019; Zarate *et al.*, 2017).

Emotional characteristics

Despite the frequent presence of a jovial disposition in SAS (Zarate *et al.*, 2017; Zarate *et al.*, 2018), individuals may show a propensity towards internalising problems such as anxiety and depression (Balasubramanian *et al.*, 2011; Cotton *et al.*, 2020; De Ravel *et al.*, 2009; Kumar & Zarate, 2020; Van Buggenhout *et al.*, 2005). High rates of anxiety (37%) have been reported by caregivers in a study with adolescents and adults (Zarate *et al.*, 2021). However, lower rates of general anxiety (17%) have been reported in a larger sample including children and adults (Bissell *et al.*, 2022), based on caregiver-report using the Anxiety Depression and Mood Scale (ADAMS; Esbensen *et al.*, 2003). Bissell *et al.* (2022) further report that 13% of individuals with SAS met cut-off for depressed mood on the ADAMS. Mental health and emotional characteristics are under-researched in SAS; this may be partly attributable to difficulties in the measurement of emotional characteristics in individuals with impaired expressive communication.

Cognitive characteristics

SAS is universally associated with developmental delay and intellectual disability with delayed language acquisition (Zarate *et al.*, 2018). Severe to profound intellectual disability is reported in over 50% of individuals with the syndrome (Zarate & Fish, 2017). Almost all individuals with SAS require assistance with activities of daily living and ongoing care (Zarate *et al.*, 2021).

Communication deficits are observed in both receptive and expressive language (Thomason *et al.*, 2019). Recent papers exploring communication found

that fewer than ten words were spoken by 84% of individuals, and 42% of individuals were non-verbal (Zarate *et al.*, 2019). Reported methods of alternative communication include the use of gestures, signs, and/or alternative augmentative communication devices; however, alternative communication skills are limited (Thomason *et al.*, 2019). Marginal strengths in receptive and non-verbal communication are reported compared to spoken language (Zarate *et al.*, 2021; Thomason *et al.*, 2019).

Genotype x phenotype correlations

Genotype-phenotype correlations are currently limited in SAS. A recent study using a 15-characteristic rubric found that large chromosomal deletions (>6 Mb) are linked to higher severity scores, particularly in neurodevelopmental domains such as adaptive behaviour/cognition, expressive communication, ambulation, behaviour, and sleep (Zarate *et al.*, 2023). Individuals with large deletions are also reported to evidence some specific characteristics, including increased feeding difficulties (Zarate *et al.*, 2023), delayed growth (Zarate *et al.*, 2019; Zarate *et al.*, 2021; Zarate *et al.*, 2023), genitourinary anomalies (Zarate & Fish, 2017), increased risk for cardiac defects (Zarate & Fish, 2017; Zarate *et al.*, 2021), and electrodermal changes (e.g., thin skin or reduced subcutaneous fat; Zarate *et al.*, 2021).

Missense variants are generally associated with lower severity scores (Zarate *et al.*, 2023), though sialorrhea (drooling/excessive salivation) is reported in a higher proportion of individuals with missense variants and other disruptive pathogenic variants (Zarate *et al.*, 2019).

Individuals with large deletions are typically diagnosed earlier (mean age 2.5 years) than those with other variants (7.6–8.3 years; Zarate *et al.*, 2019).

Life expectancy

Little is known about the life expectancy of individuals with SAS, although current research studies have included participants aged up to 37 years (Bissell *et al.*, 2022; Zarate *et al.*, 2021).

Useful websites/associations for more information

- SATB2 Gene Foundation USA: www.satb2gene.org
- SATB2 Gene Trust UK: www.satb2gene.org.uk

- SATB2 Europe: www.satb2europe.org
- SATB2 Connect Australia, New Zealand, & Asia Pacific Region: www.satb2.org.au

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Triple X Syndrome (47,XXX; TriX)

First description and alternative names

In 1959 Jacobs (Jacobs, Baikie, Brown, *et al.*, 1959) first described triple-X syndrome (TriX) in an infertile patient. The term “super female” is considered controversial (Jacobs, Baikie, Court, Brown, *et al.*, 1959). The terms triple-X syndrome, trisomy-X syndrome and 47,XXX syndrome are generally preferred. Until now, triple X syndrome has been abbreviated to TXS, but TriX is easier to pronounce.

After the first description there was a period of research in biased populations, e.g., in institutes for mentally disabled, asylums and forensic psychiatric hospitals (Olanders, 1975b). In 1974, it was decided to screen 200,000 newborns for chromosomal disorders in several hospitals. TriX cases in this study have been evaluated several times for at least 20 years. These newborn-screening studies yielded unbiased data (Robinson *et al.*, 1990). After 1990, two of these hospitals (Denver and Edinburgh) published follow-up data in young adults (Otter *et al.*, 2010). Other studies reported results from mixed-sex groups of participants and mixed groups of sex chromosome trisomies: 47,XXX, 47,XXY, and 47,XYY (Bouw, Swaab, Tartaglia, *et al.*, 2022).

Genetics and molecular biology

In TriX, there is an extra X chromosome in all cells or, in mosaic cases, in almost all cells. In other cases, there are three cell types, with XO, XX, and XXX chromosome counts (Nielsen & Thomsen, 1968; Olanders, 1975a). Today, most cases are diagnosed through prenatal diagnostic examinations (Otter *et al.*, 2021). Other girls and women may be diagnosed postnatally because of infertility/recurrent abortions, atypical development or when a family member appears to have a genetic condition (Otter *et al.*, 2021).

In 46,XX females the extra X chromosome is silenced through a process known as Lyonization, also referred to as X chromosome inactivation (XCI) (Lyon, 1961, 1962). The additional X chromosome in TriX is also silenced. In typical females, one-third of the genes on the X chromosome escape silencing (Carrel & Willard, 2005; Migeon, 2007). XCI is a dynamic

process. Diverse patterns of X chromosome regulation have been observed during development, in various tissues and diseases (Deng *et al.*, 2014; Loda *et al.*, 2022). The so-called ‘late-replicating’ X chromosome is the second X chromosome in typical women. In TriX, there is another late-replicating chromosome, resulting in an increase in replication time, which affects each cell division (Barlow, 1973). The extra X chromosome also influences nuclear architecture and epigenetic processes (Jowhar *et al.*, 2018; Kelkar & Deobagkar, 2010). Whether incomplete silencing of the extra X chromosome, prolonged cell cycle during division or epigenetic phenomena are relevant during development in 47,XXX, requires further research (Wainer-Katsir & Linial, 2019). It has been demonstrated that the extra X chromosome affects gene expression. However, there is still a need for studies that might explain the behavioural phenotype. Modern biotechnology may help elucidate the biological relationship between the extra X chromosome and behavioural patterns in TriX (Astro *et al.*, 2025; Otter, 2025a; Schulte *et al.*, 2023; Tallaksen *et al.*, 2023; Zhao *et al.*, 2025).

Incidence/prevalence

One in 1,000 females has an extra X chromosome (Jacobs, 1979).

Physical features and natural history

Tartaglia *et al.*, 2010 reviewed the physical findings in TriX. Since most of these findings (such as clinodactyly, epicanthal folds or hypertelorism) are minor physical features, most cases remain undiagnosed. Tall stature is common, and especially the underarms and legs are longer. The girls may have their growth spurt earlier than controls. Clinically speaking, decreased head circumference and smaller brains might be the most common physical features (Ratcliffe *et al.*, 1994; Serrarens *et al.*, 2022). Motor and coordination abilities seem to be somewhat retarded, and the girls are sometimes described as being clumsy (Otter *et al.*, 2010).

Since 1959 many physical disorders associated with TriX have been reported, most of which do

not exceeding the population prevalence numbers. However, some disorders seem to be more common in TriX: urogenital anomalies, (partial) epilepsy and Primary Ovarian Insufficiency (POI), Premature Ovarian Failure (POF) and infertility (Berglund *et al.*, 2022; Davis *et al.*, 2020; Tartaglia *et al.*, 2010). A recent Danish database study using clinical diagnoses and medication use in women with TriX, mosaics and controls revealed additional physical comorbidities, like gastrointestinal symptoms, including gastroesophageal reflux, constipation, and abdominal pain; dental problems; and increased risk of thrombophilia, venous thrombosis, and pulmonary embolism (Berglund *et al.*, 2022).

Behavioural and psychiatric characteristics

The behavioural phenotype is far more important than the physical phenotype. Low self-esteem appears to be the most common psychological feature in TriX (Freiling *et al.*, 2018; Otter *et al.*, 2022; Otter *et al.*, 2010). Social anxiety, shyness and executive dysfunction are common in TriX girls (Lenroot *et al.*, 2014; van Rijn, Stockmann, Borghgraef, *et al.*, 2014; van Rijn, Stockmann, van Buggenhout, *et al.*, 2014; van Rijn & Swaab, 2015). Social cognitive problems are common in TriX girls, probably due to language disorders (Bishop *et al.*, 2011; Wilson *et al.*, 2019). Developmental issues in language development have been described in TriX and other sex chromosome trisomies as well (Zampini *et al.*, 2022; Zanchi *et al.*, 2024); however, the problems seem to be slightly more severe in TriX girls. Larger groups of participants are required to investigate differences between the three different sex chromosome trisomies, and linguistic studies in adults are urgently needed (Capelli *et al.*, 2022; Zampini *et al.*, 2025). Another study in TriX girls showed a developmental pattern that resembled the development of girls with autism and mild or late presenting autism symptoms (van Rijn, Stockmann, van Buggenhout, *et al.*, 2014). Numerous studies have been conducted in toddlers and very young children to investigate issues in social communication and social interaction, as well as the regulation of emotion, cognition, and behaviour (Bouw, 2023; Kuiper, 2023; Urbanus, 2022; van Rijn *et al.*, 2023). Externalising behaviours, such as challenging behaviour, may be the result of any of these developmental difficulties and

are more common in TriX than in controls (Otter *et al.*, 2022; Otter *et al.*, 2012). However, early recognition of limitations in social functioning, social cognition and linguistic limitations may enable early intervention (Bouw, 2023; Bouw, Swaab, & van Rijn, 2022). As in linguistic studies, larger groups of participants are required in this field to investigate differences between the three different sex chromosome trisomies. The TriX girls seem to be less able to cope in a stressful environment. TriX girls living in a stable family function better than those in an unstable family (Netley, 1986). After leaving school, most TriX girls will find a job that reflects their non-verbal abilities (Robinson *et al.*, 1990). Adults might face occupational problems (Attfield, 2020, 2021; Otter *et al.*, 2012; Stochholm *et al.*, 2013). However, a more benign perspective was shown in a study among American veterans (Davis *et al.*, 2024).

There appears to be a higher prevalence of psychiatric illness in general in TriX. A study from Germany demonstrated that the extra X chromosome may influence mental health and well-being from childhood into adulthood. This study made clear that about half of the women with TriX do not experience major mental health problems (Freiling *et al.*, 2018). A recent study in a larger group of adults with TriX confirmed this (Otter *et al.*, 2022). This study showed a higher prevalence of major depressive episodes (43.3%), psychotic disorders (29.4%), suicidality (23.5%) and frequent increased levels of anxiety. Impaired social functioning was found to be an important risk factor for psychotic disorders, affective disorders, trait anxiety, and low self-esteem (Otter *et al.*, 2022). This Dutch study revealed no differences between women with TriX and controls in psychiatric medication use (Otter *et al.*, 2022), which contrasts with the results of a Danish study, which showed slightly higher levels of psychiatric medication use, especially antipsychotics and medication used for ADHD (Berglund *et al.*, 2022).

Neuropsychological characteristics

Data on intelligence in girls and adolescents are consistent, indicating that the full-scale IQ is approximately 20 points lower in these girls than expected within their families (Otter, 2025b; Robinson *et al.*, 1990). Whether the girls exhibit problems in reading or arithmetic is not uniformly reported in

the case reports and has not been confirmed in adults (Otter, 2025b). Clinical experience suggests that some difficulties during arithmetic lessons result from language disorders. Mild or severe academic problems/special educational needs are common (Attfield, 2020; Bishop *et al.*, 2011; Robinson *et al.*, 1990). Further research is needed to confirm the findings on the increased prevalence of attention problems and explain these attention problems: are they due to receptive language disorder, auditory processing disorders, anxiety disorders, attention deficit disorder (ADD) or even epilepsy (Lenroot *et al.*, 2014; Otter, 2025b; Tartaglia *et al.*, 2012)? Clinical experience treating ADD with medication suggests that the treatment is less effective than in 46,XX cases; however, controlled treatment studies are lacking. A recent study in adults revealed that women with TriX score lower in general intellectual functioning and exhibit impairments in motor processing speed and attention compared to controls, but do not differ in executive functioning, except for the women with TriX and impaired social functioning (Otter, 2025b). Women with TriX performed worse on an Emotion Recognition Task, particularly concerning recognising sadness, fear and disgust, so-called negative emotions (Otter, 2025b; Otter *et al.*, 2021).

Findings from neuroimaging studies

Neuroimaging findings in girls with an extra X chromosome demonstrated affected brain regions and related phenotypic characteristics such as language delay (thinner cortex was found in the lateral temporal lobes related to language functions), poor executive function and heightened anxiety (increased thickness in the medial temporal lobe in the vicinity of the amygdala, a region important for social cognition and linked to anxiety) through differences in cortical thickness (Lenroot *et al.*, 2014). Poor executive function and frontal lobe abnormalities have been suggested to be related (van Rijn & Swaab, 2015).

Two groups have recently published on neuroimaging in sex chromosomal disorders. The first group, from the National Institute of Mental Health, examined the impact of extra X or Y chromosomes in a group of adolescents and young adults. The second study, a Dutch case-control study in 22 adults with

TriX, focused on adults (Serrarens, 2024). The impact of the extra X chromosome on brain size has been confirmed in adolescents, young adults (Raznahan *et al.*, 2016), and adults (Serrarens *et al.*, 2022). These studies, for instance, have revealed changes in cortical thickness and surface areas of the brain, as well as their relationship to cognitive changes (Warling *et al.*, 2020). As social functioning is key to the behavioural phenotype of TriX, studies are warranted that further investigate the relationship between the brain and social functioning in TriX (Serrarens *et al.*, 2024). Another key feature in the behavioural phenotype is anxiety (Otter *et al.*, 2022). A very recent study revealed changes in the limbic areas and their relationship to anxiety (Domes *et al.*, 2025). These studies are of scientific importance, but to date, no clinical progress is expected from neuroimaging in individual cases (Raznahan & Disteche, 2021), and the variability in the behavioural phenotype has not yet been explained (Otter, 2025a).

Available guidelines for behavioural assessment/treatment/management

There is no evidence-based management guideline, although Otter *et al.* have proposed a guideline for medical and behavioural/psychiatric assessment (Otter *et al.*, 2010). It is our advice to use a broad set of tools when psychological complaints are present in children and to consider language impairments when composing the test battery (Capelli *et al.*, 2022; Zampini *et al.*, 2022). Furthermore, impairments in social functioning (Otter *et al.*, 2021; van Rijn *et al.*, 2023), as well as neurocognitive problems in children (Urbanus *et al.*, 2020) and adults (Otter, 2025b), should be assessed. A psychiatric interview should be included in a careful examination of children (van Rijn, 2019) and adults (Otter, Campforts, Stumpel, van Amelsvoort, & Drukker, 2022).

Useful websites/associations for more information

- **Unique**, a parents support group from the United Kingdom provides a syndrome sheet with information on physical and behavioural developmental issues: https://rarechromo.org/media/information/Chromosome_X/Disclosing_about_XXX_for_girls%20FTNW.pdf

https://rarechromo.org/media/information/Chromosome_X/Disclosing_about_XXX_for_parents%20FTNW.pdf

https://rarechromo.org/media/information/Chromosome_X/X%20inactivation%20QFN.pdf

- The AXYS website provides a lot of information: <https://genetic.org/variations/about-trisomy-x/>. Especially parents and TXS girls/women in the United States will find opportunities to meet experts, other parents and TXS girls/women. AXYS is actively involved in fundraising to support scientific research.

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Tuberous Sclerosis Complex (TSC)

First description and alternative names

Even though earlier cases exist, the first detailed description of the disorder was by Désiré-Magloire Bourneville, a French Physician, in 1880 when he described the case of a young girl with severe intractable epilepsy, intellectual disability and a 'confluent vesiculo-papular eruption on her nose, cheeks and forehead'. Neuropathology showed white, potato-like growths in the brain, referred to by Bourneville as 'tuberous sclerosis of the cerebral convolutions'. The term tuberous sclerosis *complex* was introduced by Moolten in 1942 to describe the multi-system nature of the disorder. The abbreviation 'TSC' is used (Curatolo, Moavero & de Vries, 2015).

Genetics and Molecular Biology

Occurs as a spontaneous mutation in 70% of cases. Autosomal dominantly inherited in the remaining 30% of familial cases. The disorder is associated with mutations in one of two genes, *TSC1* (on 9q34) or *TSC2* (on 16p13.3). The *TSC1* and *TSC2* proteins form an intracellular complex that links a number of intracellular signalling pathways including the AMPK pathway, the MAPK pathway and the PI3K pathway. The *TSC1-2* complex functions upstream of mTOR (mammalian/mechanistic Target Of Rapamycin). TSC mutations cause mTOR overactivation, leading to dysregulation of cell growth, proliferation and various other fundamental neurobiological processes. mTOR inhibitors have been approved by the FDA and EMA for the treatment of brain SEGAs (subependymal giant cell astrocytoma), renal angiomyolipoma, and treatment-resistant epilepsy associated with TSC. Topical preparations of mTOR inhibitors are frequently used for facial angiofibromas and other skin manifestations of TSC. Clinical trials of mTOR inhibitors are underway for neuropsychiatric features of TSC, but have so far shown mixed results, at least in part due to the highly heterogeneous nature of the behavioural phenotype of TSC (see Curatolo, Moavero & de Vries, 2015 for primary references).

Incidence/prevalence

Birth incidence of about 1 in 5,800 (Osborne *et al.*, 1991, see Curatolo, Moavero & de Vries, 2015 for primary references).

Physical features and natural history

Wide variability of expression. The previously used "diagnostic triad" (of epilepsy, intellectual disability and characteristic facial skin lesions) is seen in only about 30% of people with the disorder. TSC is multi-system and can include hamartomatous growths affecting the brain, skin, kidneys, heart, eyes, teeth, lungs and other organs. About 70-80% of people with TSC have a lifetime history of epilepsy. Diagnosis is based on meeting clinical criteria for the disorder or having a pathogenic mutation in one of the TSC genes (Northrup *et al.*, 2021). Mutations are identified in >90% of individuals with clinically confirmed TSC and mosaic mutations in a further proportion.

TSC is not an inevitably declining condition, and any deterioration in physical or neuropsychiatric profile should be further investigated. Life expectancy is influenced by the degree of physical and neurological involvement. Intractable seizures, SEGAs and renal failure secondary to angiomyolipomas may be causes of death. However, molecularly-targeted treatments with mTOR inhibitors are now available for many of these manifestations (see Curatolo, Moavero & de Vries; de Vries, Wilde *et al.*, 2018 for primary references).

Behavioural and psychiatric characteristics

Tuberous Sclerosis is associated with a wide range of behavioural, psychiatric, intellectual, academic, neuropsychological and psychosocial difficulties. The term 'TAND' (TSC-Associated Neuropsychiatric Disorders) was coined in 2012 as an umbrella term for all the bio-psycho-social aspects of the disorder (de Vries *et al.*, 2015) and a TAND Checklist has been developed to aid clinical teams to screen for TAND (de Vries *et al.*, 2015; Leclézio *et al.*, 2015). In 2023 a self-report, quantified TAND Checklist (TAND-SQ) was published (Heunis *et al.*, 2023). At the behavioural level, TSC is associated with high rates of mood/anxiety, overactive/impulsive, sleep/eating, dysregulated behaviours (aggression and tantrums), and many autism-related behaviours. At the psychiatric level, neurodevelopmental disorders are common, with autism spectrum disorders (ASD) in 40-50%, ADHD and attention-related disorders in 30-50% and intellectual

disability in ~50% of individuals. TSC is one of the medical conditions most commonly associated with ASD. In adolescents and adults, very high rates of anxiety and mood disorders are reported. Psychotic disorders should raise the possibility of seizure-related psychopathology (de Vries *et al.*, 2015).

Neuropsychological characteristics

At the intellectual level, more than 50% of individuals with TSC will have global intellectual abilities in the normal range, but often with an uneven profile of strengths and weaknesses. Intellectual abilities tended to show a bimodal distribution in TSC where 30% of individuals with TSC had profound global intellectual disability (IQ equivalent <20) and the remaining 70% fell on a normal distribution curve, shifted to the left. Interestingly, the bimodal distribution of IQ has become less pronounced in TSC research studies over the last decade. At the scholastic/academic level, almost 60% of people with TSC will have a history of reading, writing, spelling or mathematics difficulties (de Vries *et al.*, 2018; de Vries, Wilde *et al.*, 2018). At the neuropsychological level, there are high rates of specific neuropsychological deficits, even in those with normal or high global intellectual abilities. Specific deficits are most prominent in attentional, executive and visuo-spatial skills. These neuropsychological deficits may be associated with significant impairment of functional abilities in daily life (de Vries, Wilde *et al.*, 2018; Curatolo, Moavero & de Vries, 2015; de Vries *et al.*, 2015).

Available guidelines for behavioural assessment/treatment/management

- International consensus guidelines were drawn up for the assessment of cognitive and behavioural problems in TSC (de Vries *et al.*, 2005). These were revised and are augmented by the new guidelines on screening and assessment (Krueger, Northrup *et al.*, 2013) and by the TAND Checklist (de Vries *et al.*, 2015; Leclezio *et al.*, 2015). The most recent update of diagnostic criteria and treatment guidelines were published in 2021 (Northrup *et al.*, 2021).
- There are currently no TSC-specific treatments available for the neuropsychiatric manifestations of TSC. Clinicians should therefore use evidence-based interventions as for the general population.

International consensus recommendations for the identification and treatment of TAND is expected in 2023.

- Targeted treatments using mTOR inhibitors are currently in clinical trials for TSC-associated neuropsychiatric disorders (TAND) (Curatolo, Moavero & de Vries, 2015; de Vries, Wilde, *et al.*, 2018), but these are not at present recommended outside clinical trials.

Useful websites/associations for more information

- www.tuberous-sclerosis.org
[UK user/carer organization]
- www.tscalliance.org
[USA user/carer organization]
- www.tscinternational.org
[International user/carer organization]
- www.tandconsortium.org
[International TAND research consortium]

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Petrus J de Vries & Anna Jansen, Updated July 2023

Turner syndrome

First description

Henry Turner first described Turner syndrome in 1938, but it was not until 20 years later that the genetic basis of the syndrome was discovered. About 50% of clinically identified cases of Turner syndrome are associated with a single X chromosome (X-monosomy, XO), and affected females therefore have 45 rather than the usual 46 intact chromosomes. Typical females have two completely intact X-chromosomes. Typical males have one X-chromosome and a Y chromosome which contains the male-sex determining gene. To develop typically, females need to express some critical genetic material from both their intact X-chromosomes in just the right amount, not too little and not too much.

Genetics and molecular biology

Because Turner syndrome females typically have just one sex chromosome in all the cells of their body, the Turner syndrome phenotype (the physical and mental features that are characteristic of the syndrome) arises because there is too little genetic material from genes that are normally expressed from both X-chromosomes. Some of the features are caused directly by that insufficiency, and some are secondary to early degeneration of the ovaries and the consequent oestrogen insufficiency which leads to immature secondary sexual characteristics. Surprisingly, we know rather little about which genes on the X-chromosome are needed in two copies for typical development. To date, the only gene that is clearly linked to the syndromic features is called SHOX, and it is responsible for the limited growth in stature.

Turner syndrome is usually associated with just one intact X-chromosome, and the second X-chromosome is missing altogether in cells throughout the body. In ~70% of X-monosomy, the missing X chromosome came from the father. Typical females inherit one X-chromosome from their father, and one from their mother. In just less than half of clinically identified females with Turner syndrome there is more than one chromosomal rearrangement. One X-chromosome is intact but there is a second X-chromosome too, but that second X is incomplete, and can be structurally

very unusual so that it does not function properly. To complicate matters further, about half of all females with Turner syndrome have a mixture of cell-types in their body, and we call this 'mosaicism'. Females with a mixture of X-monosomic cells (45,X) and typical female cells (46,XX) are likely to have mild features of the syndrome and may not even be diagnosed unless they are investigated genetically, for instance because of infertility.

Physical features and natural history

There are many possible physical characteristics of the syndrome, but none is invariable. The condition may be detected at birth, suspected because of a transient edema (tissue swelling) of the lower legs and feet. It rapidly clears up, and if not recognised at the time the diagnosis may not be made until middle childhood. The usual reason for further investigations is growth delay.

Specific characteristics include a narrow, high-arched palate, which is associated with severe feeding difficulties in infancy. These are not only due to the palatal problem but also to oromotor immaturity. There are low-set ears, a low hairline, and occasionally a webbed neck (this latter feature being much rarer than textbook descriptions would suggest). The eyes may show strabismus (a squint) and a slight ptosis (droopy eyelids). The chest is typically broad, with widely spaced breasts. When standing with arms at the side, the lower arms typically turn out at the elbows (described as a wide carrying angle).

Some form of cardiac abnormality occurs in approximately one-third of Turners patients. Problems are primarily left-sided and may include coarctation of the aorta and bicuspid aortic valve. Individuals with Turner syndrome are also at higher risk for hypertension and should receive an echocardiogram or MRI to evaluate the heart at the time of diagnosis regardless of age.

Other common problems include renal anomalies (30%) associated with an increased risk of urinary tract infections and hypertension. Hypothyroidism is associated with an autoimmune thyroiditis. One of

the most serious, but often overlooked, complications is recurrent otitis media, exacerbated by anatomical anomalies of the Eustachian tube. This is extremely common, and occurs in up to 80%. The onset is later than in typical children, between 4-15 years of age. Aggressive treatment of infections is appropriate. The majority (50-90%) of women with Turner syndrome will also develop early sensorineural (nerve) hearing loss, with gradual deterioration from childhood. They may require hearing aids earlier than the general population.

Because of the small stature, which is almost invariable relative to the height of the parents, it has become usual to treat with human growth hormone. The average stature after treatment is increased by a few centimeters, although the condition is not associated with growth hormone insufficiency and high doses are needed to achieve any significant benefit. There is no evidence that treatment with growth hormone benefits psychosocial adjustment, although it may improve self-esteem.

Behavioural and psychiatric characteristics

Social integration is usually good until adolescence. The normal adolescent growth spurt does not come along as expected, and secondary sexual characteristics do not appear. Most girls with Turner syndrome mature under the influence of endocrinological management (oestrogen supplementation). Physical immaturity can be associated with difficulties integrating with a typical peer group during early adolescence. Associated behavioural immaturity may be encouraged because such girls are 'babied' by others.

Social difficulties usually begin in adolescence. The most important contributory influence is a lack of social confidence. For reasons that are likely to be a combination of genetic and hormonal deficiencies, development of the 'social brain' is impaired. At least one in three girls begins to experience social difficulties during the teenage years. Forming and maintaining peer relationships becomes more problematic than it was at primary school, because girls' social relationships become more complex during adolescence. Social difficulties can persist until adulthood. Many women with Turner syndrome

find it hard to function effectively in complex social or work environments where they are expected to communicate with lots of adults. A substantial minority choose to take jobs focused on child-care (especially nursery nursing) in the UK.

Many females with Turner syndrome have poor self-esteem, especially in later life. Social anxiety and lack of confidence is made worse by difficulties establishing satisfactory social relationships. Their social problems are compounded by the onset of associated hearing loss.

Turner syndrome is associated with life-long social adjustment problems, but these are not directly caused by short stature or infertility. They will not be resolved by growth-hormone treatment, although this may have other benefits. There is an increasing acknowledgement among Turner syndrome support groups and clinicians responsible for their care that the symptoms of a mild autism spectrum disorder (ASD) are common and that it is the social communication difficulties inherent in the condition that impact most strongly on friendships and family relationships. Females who are missing a fully functioning second X-chromosome are at increased risk of failing fully to understand other people's social cues and responding appropriately. They may also be rather rigid and resistant to change or new experiences.

Neuropsychological characteristics

Almost all females with the syndrome have normal verbal intelligence. About 80% have relatively poor visuospatial memory (in the lower 33% of ability relative to the general population). This can have practical consequences, such as a tendency to lose one's way in unfamiliar environments. Some motor skills may be impaired; clumsiness is typical, especially in fine motor tasks. Very poor arithmetical abilities, found in the majority, reflect slow processing speeds and a fundamental conceptual problem with comprehending numerical magnitude (e.g. being able quickly to recognise that 9 is half as big again as 6).

Socio-perceptual processing is impaired to some extent in at least one third, with difficulties remembering faces or differentiating facial expressions of emotion. Socio-cognitive anomalies in Turner syndrome extend to deficits in mentalizing abilities.

In common with females who are on the autism spectrum, girls with Turner syndrome attempt to compensate for their social deficits from early childhood. They develop superficially good and engaging social skills, which are learned from imitation, but may become associated with social disinhibition. Poor attention is typical during early and middle childhood, leading to the appearance of attention deficit hyperactivity disorder. This often resolves by adolescence. On the other hand, social naivety persists and puts many affected women at risk of exploitation.

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Updated: David H Skuse & Jeanne Wolstencroft,
March 2025

Available guidelines for behavioural assessment/treatment/management

- Gravholt C.H., et al., Clinical practice guidelines for the care of girls and women with Turner syndrome: Proceedings from the 2023 Aarhus International Turner Syndrome Meeting, European Journal of Endocrinology, Volume 190, Issue 6, June 2024, Pages G53–G151, <https://doi.org/10.1093/ejendo/lvaeo50> Gravholt C.H.(2009) "Turner – know your body!" Editor –Published by Novo-Nordisk. Available as a free web-publication <http://np.netpublicator.com/netpublication/n75088268>

Useful websites/Associations for more information

- Turner syndrome support society (UK): <http://www.tss.org.uk/>
- National Institute of Child Health and Human Development (USA): <http://turners.nichd.nih.gov/>

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22q11.2 Deletion Syndrome (Velo-Cardio Facial Syndrome)

First descriptions and alternative names

As is so often the case, chromosome **22q11.2 deletion syndrome (22q11.2DS)** was first described independently by several perceptive clinicians back in the 1950s to 1970s. As these clinicians were experts within different specialties and therefore not focussing on the same medical problems, several constellations of features were described as separate conditions. The first person to describe children who most likely had 22q11.2DS was the otolaryngologist (i.e. ear nose and throat specialist) Eva Sedláčková who already in 1955 described children with hypernasal speech associated with a congenitally shortened soft palate, facial dysmorphology and intellectual impairments [1-4]. She was later to show that many of these children also had cardiac malformations and submucous clefts. Following Sedláčková's observations, other clinicians such as the endocrinologist Angelo DiGeorge (first English publication) described children with presentations of immunodeficiency, hypoparathyroidism and congenital heart disease [5], the physician Kinouchi described children with cardiac abnormalities and a typical face [6] and the speech-language pathologist Robert Shprintzen described children with cleft palate, cardiac anomalies, a typical face and learning problems [7]. To avoid confusion, the syndrome is nowadays typically referred to as 22q11.2 deletion syndrome, a description based on its underlying genetic cause, however **alternative names for the syndrome are velo-cardio-facial syndrome (VCFS), velofacial hypoplasia, Sedláčková syndrome, DiGeorge syndrome, Shprintzen syndrome, Cayler syndrome, conotruncal anomaly face syndrome and cardiac defects, abnormal facial features, thymic hypoplasia, cleft palate, and hypocalcemia (CATCH 22).**

Genetics/aetiology

Whilst visible cytogenetic deletions were identified in about one quarter of children with DiGeorge syndrome in the mid-1980s, it was not until the early 1990s that the microdeletions of chromosome 22q11.2 was identified as the cause of most cases of DiGeorge syndrome and that indeed, children with other

groupings of symptoms, including most of those with VCFS, were found to share the genetic aetiology [8, 9]. Whilst the microdeletions vary in size, the deletion typically encompasses 0.7 to 3 million base pairs, a region that contains approximately 50 genes. The majority of people diagnosed with 22q11.2DS have a de novo or spontaneously occurring deletion and a smaller proportion (about 15%) have an inherited deletion. The deletion is inherited in an autosomal dominant manner, meaning that if a person has the deletion there is a 50% chance that the deletion will be passed on to their offspring.

Incidence/prevalence

Generally the prevalence of the syndrome is described to be 1 in 2148 live births and 1 in 992 pregnancies [10, 11]. However, it has been argued that the syndrome is still clinically under-recognised with many older individuals diagnosed when they themselves have children diagnosed with the syndrome [12, 13]. Whilst most people, including many health care professionals, have not heard of 22q11.2DS it is the most common cause of syndromic palatal anomalies and also one of the most common causes of congenital heart defects and developmental delay [13]. It is also likely that the prevalence of the syndrome will rise as mortality decreases and reproductive fitness increases [14, 15]. The syndrome affects individuals of both sexes and of different ethnic background equally [16] although it has been suggested that there are sex differences in the expression of the syndrome [e.g., 17, 18].

Physical characteristics

22q11.2DS is a multisystem disorder including more than 180 characteristics. However, there is a large variability in the expression of the phenotype even amongst members of the same family and characteristics can range from life threatening to very mild [19]. The most common features include congenital heart defects (including conotruncal anomalies), thymic hypoplasia/aplasia, palatal anomalies (including submucous cleft palate and/or velopharyngeal incompetence); immunodeficiency;

hypocalcaemia; vascular anomalies; feeding difficulties; gastrointestinal issues; scoliosis; sleep disorders; hypotonia and subtle, but characteristic, facial features [9, 13, 20]. Due to the multisystemic impact of 22q11.2DS, it is important that each individual has an individualised care plan involving a multidisciplinary health care team.

Cognitive characteristics

Whilst there is a large variability within the cognitive profile of individuals with the syndrome, cognitive impairments are very common and are associated with learning problems. Intellectual functioning typically range from low average to mild intellectual disability with the majority of individuals having an intellectual ability in the borderline range [21]. Typically, verbal intellectual functioning decline slightly with increased age but more so in the presence of psychosis [22]. Specific cognitive impairments in executive functioning, memory, working memory, sustained attention, visual-spatial processing are common [e.g., 23, 24]. In addition, individuals with the syndrome have been found to have deficits in social cognition including problems in interpreting facial expressions, theory of mind and social perception [e.g., 25, 26-28]. Problems with understanding maths are common in 22q11.2DS and specific learning disorders including mathematics (dyscalculia) are often diagnosed with significant impact on daily living skills [29].

Behavioural characteristics

Emotion dysregulation is a commonly occurring difficulty for people with the syndrome. There has been reports that children and adults experience both internalising and externalising behaviours with early reports suggestive of extremes of behaviour including temper outbursts as well as shyness and withdrawal [30]. A recent paper found that while some people with 22q11.2DS have not difficulties with emotion regulation, other people may predominantly have either internalising or externalising problems or a combination of the latter [31]. Overall, it was found that externalising problems including aggression is associated with having more difficulties in everyday life. People with 22q11.2DS who also have emotion regulation difficulties are more likely to have diagnoses

of autism, attention deficit hyperactivity disorder, anxiety or depression [32, 33]. Adults who also have a diagnosis of schizophrenia are also at an increased risk of aggressive behaviours [34, 35].

Social relationships can be problematic for people with 22q11.2DS, there has been reports of difficulties with social skills and social-cognition that may make it more difficult to initiate and maintain friendships as well as understanding social dynamics [36]. This may be further complicated by emotion dysregulation and more general cognitive difficulties. There has also been reports that many people with the syndrome are victimised or bullied at school with clear impacts on mental health and wellbeing [37].

Mental Health and Wellbeing

Children with 22q11.2DS are at higher risk of being diagnosed with psychiatric disorders such as attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder, anxiety disorders (generalised anxiety disorder, separation anxiety, and phobias) and autism [38]. It has been proposed that as many as 60-70% of children with 22q11.2 have at least one diagnosed psychiatric disorder. In late teenage years and early adulthood there is an increased risk of depressive disorders and also a high risk of psychotic disorders including schizophrenia. Low full-scale IQ (FSIQ) in childhood, early cognitive decline, and inattentive symptoms have been found to be risk factors for the development of psychotic symptoms [22, 39]. However, conduct disorder and substance use disorder diagnoses are rare in the syndrome. Most of the psychiatric disorders persist into adulthood [20]. Many people with the syndrome have more than one psychiatric diagnosis, highlighting the complexity of care [38]. There are indications in the literature that despite the high prevalence of psychiatric disorders, many individuals with 22q11.2DS are not receiving the appropriate psychiatric care [40]. It is also important to note that psychiatric symptoms are likely to be impacted by sleep disorders and fatigue that are common in the syndrome and that has a significant impact on quality of life [41-44].

Family functioning

Parents of children with 22q11.2DS report higher levels of parenting stress and poorer mental health compared to parents of typically developing children [45, 46]. Parents often struggle with managing concerns related to their child's diagnostic journey, interactions with the health care system, education and mental health [47, 48]. The concerns of parents often change over time with an initial focus on the health care needs and speech issues of children in early childhood, changing to a focus on intellectual, learning, social and anxiety related issues in mid-childhood. Around this age there are also increasing concerns about independence and mental health [49]. There has been suggestions that, as in other similar conditions, there is an association between parental stress and mental health and child outcomes [45, 46, 50]. It is important to remember that in order to look after a person with 22q11.2DS well, it is important to consider the whole family system [48].

Available clinical guidelines

- Updated clinical practice recommendations for managing children with 22q11.2 deletion syndrome
- Updated clinical practice recommendations for managing adults with 22q11.2 deletion syndrome

Useful websites/associations for more information

- International 22q11.2 Foundation
<http://www.22q.org/>
- 22q11.2 Society
<http://www.22qsociety.org/>
- 22q Foundation Australia and New Zealand
<https://www.22q.org.au/>

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Linda Campbell : July 2023

CONTENTS

PROGRAMME

ABSTRACTS

SYNDROMES

Williams Syndrome (also known as Williams-Beuren Syndrome)

First descriptions:

The syndrome was first described by Williams *et al.* (1961) in four patients with supravulvar aortic stenosis (SVAS) in association with intellectual disability and an unusual facial appearance, and by Beuren *et al.* (1964). Black and Carter (1963) associated this characteristic facial appearance with that found in idiopathic infantile hypercalcaemia, a name initially used for the syndrome.

Genetic aspects:

Williams syndrome is a genetically determined neurodevelopmental disorder caused by a heterozygous deletion of about 1.6 Mb (approx. 26 – 28 genes) on chromosome 7 (7q11.23). A deletion of the elastin gene (ELN) which occurs in >99% of individuals with WS) is associated with congenital heart disease and connective tissue abnormalities including hernias and premature ageing of the skin. Several genes are also implicated in the intellectual disabilities and cognitive deficits observed in WS, including GTF2I, LIMK1 and CYLN2 (see Kozel *et al.*, 2021; Morris, 2017; Morris & Mervis, 2021, 2017 for reviews). Transmission is autosomal dominant and although most cases are de novo occurrences, some instances of parent to child transmission have been reported (Donnai & Karmiloff-Smith, 2000).

Incidence:

The condition is estimated to occur in 1 per 20,000 individuals although higher rates (1 in 7500) have been reported (Kozel *et al.*, 2021).

Physical phenotype and natural history:

The condition typically presents in infancy with difficulties in feeding, irritability, constipation and failure to thrive. The physical phenotype is remarkably consistent across the world (Kruszka *et al.*, 2018) and the principal characteristics are well summarised by Kozel *et al.*, (2021). The main features include: endocrine and growth abnormalities (pre-natal growth deficiency, failure to thrive in infancy, infantile hypercalcaemia, hypercalciuria, hypothyroidism, early

puberty); cardiovascular disease (mainly supravulvar aortic stenosis) and renal abnormalities; connective tissue abnormalities (hoarse voice, inguinal/umbilical hernia, bowel/bladder diverticulae, rectal prolapse, joint and skin laxity), and distinctive facies (broad brow, short nose, long philtrum, bitemporal narrowness, periorbital fullness, full lips, wide mouth, malocclusion, small jaw and prominent earlobes).

With age, subcutaneous tissue is lost, giving rise to a prematurely aged appearance. Premature greying of the hair occurs in many adults. A characteristic posture may develop with sloping shoulders, exaggerated lumbar lordosis and flexion at the hips and knees. Progressive multi-system medical problems have been reported in some adults, which can lead to premature death. These include cardiovascular complications, gastrointestinal problems and urinary tract abnormalities. Progressive joint limitations are also common.

Behavioural and psychological characteristics:

Most individuals have moderate to mild intellectual impairments, although some may be of low-average to average IQ (Royston *et al.*, 2019). Overall cognitive ability generally remains fairly stable across the life span (Kozel *et al.*, 2021) but verbal IQ is typically higher than non-verbal IQ and there are complex, and often subtle, pattern of peaks and valleys within each of these domains. Research into the nonverbal abilities of individuals with WS has highlighted particular deficits in domains such as number skills, planning, problem solving and spatial cognition. In contrast, face processing and some aspects of social cognition tend to be relative strengths. Within the verbal domain, auditory rote memory and receptive vocabulary are viewed as strengths, while spatial language (e.g. using spatial terminology), expressive vocabulary, syntax, semantics and grammatical comprehension are generally delayed (see Royston *et al.*, 2019 for review); pragmatic language difficulties may also become more apparent with age (Van Den Heuvel *et al.*, 2016). Adaptive behaviour skills are often relatively poor (Fu *et al.*, 2015; Howlin *et al.*, 2010) but research findings

on the association between IQ and adaptive behaviour are inconsistent. Profiles of adaptive functioning also vary with age although Social/Communication skills tend to be more advanced than Daily Living Skills, especially in children and adolescents (Brawn and Porter, 2018).

Individuals with WS tend to show particular patterns of emotional and behavioural difficulties (Einfeld *et al.*, 2001; Morris, 2017). An intense drive for social interaction is one of the most characteristic traits and is evident from early childhood (Riby *et al.*, 2017). However, older children and adults with WS have difficulties making and sustaining friendships and because of their desire to make social contact they have a high risk of being bullied, exploited or abused (Fisher *et al.*, 2017; Fisher & Morin, 2017). Other difficulties include hyperacusis, attentional problems, impulsivity, and externalizing (oppositonality and aggression) and internalizing problems (anxiety and withdrawal) (Klein Tasman *et al.*, 2017; Royston *et al.*, 2019). A significant minority of children shows autistic-type symptoms (social communication deficits, stereotyped and repetitive behaviours; Klein Tasman *et al.*, 2018); however, reported rates of self-injurious behaviours are lower than in other genetic developmental disorders (Huisman *et al.*, 2018).

Rates of mental health problems in adulthood are high and include phobias, preoccupations and obsessions, depression, bipolar disorder and hypomania. The most commonly reported mental health problem is anxiety, which occurs more often in WS than in individuals with other developmental genetic disorders and is significantly more frequent than in the general population (Royston *et al.* 2017).

Further information

- www.williams-syndrome.org.uk

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Patricia Howlin, 2019
Updated by Stewart Einfeld
and Patricia Howlin, 2023

Wolf-Hirschhorn syndrome

Wolf-Hirschhorn syndrome (WHS) is a multiple congenital malformation syndrome first described in 1965 independently by Cooper and Hirschhorn and by Wolf, which presents with a broad range of complex clinical manifestations and variability, but also with a variability both in terms of deletion size and and causal process. It is caused by a partial loss of genetic material at the telomere of the short arm of chromosome 4 and, specifically, from a deletion of the terminal 2 Mb of the 4p16.3 region (Figure 1) although the hemizygosity can be variable in size and etiology. The high variability present at both clinical and molecular level can cause difficulties in diagnosis of WHS.

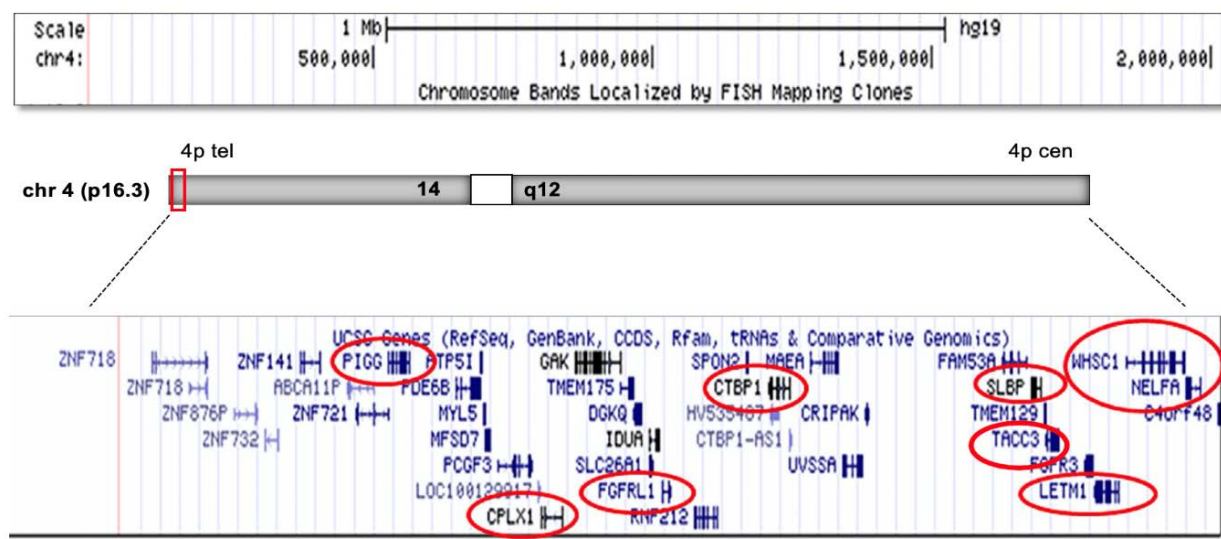


Figure 1. Diagram showing the distal region of chromosome 4p, where candidate genes for seizures and craniofacial features map (LEMT1 and WHSC1; Zollino *et al.*, 2003; Rodriguez *et al.*, 2005). [Diagram was modified from Battaglia *et al.*, 2015].

Genetics and Molecular Biology

The genotype often arises from an unbalanced translocation event (t(4;8) (p16;23). Most often, however, the genotype is produced by a *de novo* mutation. The mechanism(s) which produce the deletion are not known, but recent studies suggest that genes within sub-telomeric regions are likely to be involved in deleterious chromosomal rearrangements. Deletion size in WHS varies; it is most often telomeric, but it can also be interstitial. It is usually detected by conventional karyotyping or fluorescence *in situ* hybridization (FISH) (50-60%) but chromosomal microarray analysis (CMA) is considered the gold standard technique for WHS diagnosis..

de novo microdeletions account for approximately 25–30% and, unbalanced translocations (*de novo* or inherited) and complex genomic rearrangements, as ring 4 chromosome, are observed in approximately 15% if the cases (Battaglia *et al.*, 2001; 2009; Lurie *et al.*, 1980). However, it has been suggested that the prevalence of unbalanced translocations leading to WHS is underestimated as they could be missed by karyotyping and FISH (South *et al.*, 2008). Submicroscopic deletions are also observed in WHS and often identified by multiplex ligation-dependant probe amplification (MLPA) and/or by CGH arrays (Ho *et al.*, 2016; Wright *et al.*, 1997). The size of the deletion has been associated with the severity in the phenotype and results, in part, to the wide variability of the clinical presentation. For a complete WHS diagnosis in the proband, chromosomal analysis is recommended also for the parents, in order to establish the risk of recurrence of other family members. Taken all together these

observations point toward a mandatory use of several genetic investigations (CMA, MLPA, FISH, karyotype) for a complete diagnosis of WHS, in addition to chromosomal analysis of the parents for assessing the risk of occurrence of other cases in the family. A combination of MLPA with CMA can provide a comprehensive approach to diagnosing WHS, ensuring that both large and small deletions are detected.

Twelve genes identified by the human genome project between 1.2 and 2.0Mb from the telomere of 4p, five (WHSC1, WHSC2, TACC3, SLBP and HSPX153) are suspected of encoding proteins involved in mRNA processes or transcription. Recent exome sequencing analyses led to the identification of two genes within the (WHSCR): the WHS candidate gene 1 (WHSC1), also known as nuclear receptor-binding Set Domain-protein 2 (NSD2), contained only partly within the WHSCR (Derar *et al.* 2019), and WHS candidate gene 2 (WHSC2), also known as Negative Elongation Factor Complex Member A (NELFA), entirely contained within the WHSCR (Cyr *et al.* 2011). Specifically, two minimal critical regions, have been identified corresponding to the smallest region, whose haploinsufficiency leads to the core WHS phenotype (Rauch *et al.* 2001; Zollino *et al.* 2003; Rodriguez *et al.* 2005). Furthermore, WHSC1 and SLBP genes, are both involved in histone metabolism, and therefore might affect the expression of other genes. Hence, it is likely that some of WHS pathology results from the combined effects of haploinsufficiency in more than one of these genes and generating significant biological changes in the expression of the correspondent target genes.

Prevalence and Mortality

The genotype is relatively rare – estimates of its prevalence range from 1:20,000-50,000 live births with a 2:1 female-to-male ratio (Maas *et al.*, 2008). Mortality rate in the first two years of life is high [~21%]. However, the median life expectancy for those who survive is greater than age thirty years. Nonetheless, life expectancies are far greater for other microdeletion cases than for WHS..

Physical, Behavioural and Neuropsychological Features

Clinical characteristics of the phenotype include growth delay, hypotonia, unusual idiosyncratic distinctive craniofacial appearance - “Greek warrior helmet” – that are the combined result of microcephaly, broad forehead, prominent glabella, hypertelorism, high arched eyebrows, short philtrum and micrognathia. In addition, are variable observed clinical manifestations severe feeding difficulties, and congenital anomalies like skeletal anomalies, heart lesions, oral facial clefts, senso-neural deafness, and genitourinary tract defects (Battaglia *et al.* 2001).

Most individuals with WHS are prone to seizures, have mild to profound intellectual disability, attention deficits and limited, if any, expressive speech, and language. The appearance of epilepsy [Battaglia *et al.*, 2015], in about 90-100% of the WHS cases, usually occurs in the first 3 years of life. It can be triggered by fever in about 70% of the cases [Battaglia *et al.* 2008] or due to a synergism with additional genes [Bi *et al.*, 2016]. Children with WHS are more severely impacted (~ 65% are profoundly ID) in both general cognitive ability and overall adaptive behaviour skills compared to children with other microdeletions. Among less severely affected children, i.e., those who have expressive language, the profile of mean cognitive abilities and deficits is relatively flat and extends to all cognitive areas tested: verbal, quantitative, and abstract/visual reasoning, and short-term memory. Interestingly, and despite their limitations in cognitive ability and overall adaptive behaviour, children with WHS exhibit relative competence in socialisation skills compared to their abilities in other adaptive behaviour domains (Fisch *et al.* 2010). On the other hand, they often have significant social problems, as assessed by the Conners Parent Rating Scale and Child Behavior Checklist. Limited attention span among children with WHS likely has a negative impact on their short-term memory skills. To that extent, these difficulties are not unique to the WHS phenotype. The proportion of children with WHS with autism or autistic-like features is significantly lower than the rates of autism found in the other sub-telomeric disorders such as 2q37, 8p23 and 11q22-25 (Jacobsen syndrome).

Interestingly, children who have an heterozygous deletions of the distal short arm of chromosome 4 that includes the NSD2 gene tend to present a milder spectrum of skeletal abnormalities, and exhibit fewer seizures.

In summary, WHS is a complex genetic disorder with a known genetic aetiology, variable expressivity, and penetrance, thus a wide spectrum of clinical involvements and clinical manifestations are observed. Although the variability in the broad range clinical manifestations observed in WHS, can be in part explained by the extent of the deletion, it is more likely that a synergistic effect of the haploinsufficiency of the genes mapping within the deleted area and additional factors including genetic backgrounds, allelic variation in the non-deleted regions of the other chromosome 4 and unbalanced translocation (Zollino *et al.* 2000; South *et al.*, 2008) lead to the observed heterogeneous phenotype. Although the common features include intellectual disability, facial features, growth delays, and seizures are common, recent studies have underlined the existence of milder phenotypic forms, such of those in which the NSD2 gene is involved.

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Updated in 2025 by Flora Tassone

47,XYY Syndrome

First description and molecular biology

47,XYY syndrome; Jacob's syndrome. The first case of XYY syndrome was reported as an incidental finding by Adam Sandberg and colleagues in 1961. Four years later, Patricia Jacobs, a British geneticist, further researched this chromosome aneuploidy and described it in great detail; thus, the presence of an extra Y chromosome is also called Jacob's syndrome.

Genetics and molecular biology

The majority of cases of XYY syndrome are due to a paternal non-disjunction during meiosis II, following a normal meiosis I. In some cases, it arises during early embryogenesis in a postzygotic mitotic error, in which case it can result in a 46,XY/47,XYY mosaic form (Robinson & Jacobs, 1999).

Incidence/prevalence

The prevalence of 47,XYY is currently estimated at approximately 1:1000 males. Since 47,XYY is typically not associated with marked phenotypic characteristics, it remains frequently under-detected with 90% of cases never diagnosed in their lifetime (Abramsky & Chapple, 1997). Of those diagnosed, most cases are diagnosed postnatally and late in life. However, the incidence of prenatal detection of 47,XYY may be increasing due to non-invasive prenatal screening (NIPS). Results of this screening should be confirmed prenatally (via amniocentesis or chorionic villus sampling) or postnatally (via chromosome karyotype analysis performed by a blood sample or by a chromosomal microarray). A chromosomal microarray (CMA) test can consist of an oral cheek (buccal) swab or blood test. A cheek swab is an easy and painless way to detect chromosomal abnormalities and provide a definitive diagnosis.

Physical features and natural history

Physical phenotypic differences associated with 47,XYY syndrome are usually mild. Hypertelorism (wide spaced eyes), macrodontia, pes planus (flat feet), central adiposity, clinodactyly, and larger head circumferences than typically developing boys have

been described in boys with this disorder (Bardsley *et al.*, 2013; Lalatta *et al.*, 2012). Speech delays are common. Motor developmental delays in sitting and walking, decreased muscle tone (hypotonia), and behavioural and emotional difficulties may occur. Boys have increased growth velocity during childhood, and adult height is usually increased by approximately 7cm (3in) above what is expected (Aksela *et al.*, 2008). 47,XYY men are usually taller than 1.85m or 6 ft 5 inches, and the tall stature can be explained by the presence of additional copies of the SHOX gene (and possibly also other genes related to stature). Cystic acne may develop during adolescence. Asthma prevalence is greater in 47,XYY than in the general population (Bardsley *et al.*, 2013).

For adolescents with 47,XYY puberty proceeds normally and there are typically no issues related to testicular function nor fertility, as opposed to boys with 47,XXY (KS) who experience testicular failure. A trend of macroorchidism has been noted during early puberty for boys with 47,XYY (Bardsley *et al.*, 2013).

Behavioural and mental health characteristics

Individuals with 47,XYY syndrome may be at increased risk for behavioural problems and mental health issues. There is an increased rate of attention deficit hyperactivity disorder (ADHD) [more marked than in 47,XXY (KS)], and increased risk of challenges within classroom behaviour. Problems with social interactions with peers and in confrontational situations are also common. Individuals with 47,XYY have been reported as having increased scores on measures of autistic spectrum disorders (ASD) symptoms, however, previous studies have been confounded by many factors. Further investigation is necessary before a definitive answer can be given on the association of ASD and 47,XYY. ASD is a highly inheritable genetic disorder; therefore, multigenerational family histories should be completed in order to determine familial risk for ASD.

Prenatal diagnosis was associated with higher cognitive function and less likelihood of an ASD diagnosis (Ross *et al.*, 2015). Further, the expression

of NLGN4Y, a gene that may be involved in synaptic function, is increased in boys with 47,XYX when compared to the neurotypical 46,XY controls (Ross *et al.*, 2015). Psychiatric diagnoses are more common in boys diagnosed postnatally and are often the reason these boys had karyotype evaluation (Bardsley *et al.*, 2013). Risk for psychosis may be increased in men with 47,XYX (Verri *et al.*, 2008). The importance of this finding has not been determined in the neurodevelopment of the boy with 47,XYX.

Developmental delays, behavioural dysfunction, and mental health disturbances may be more common in boys diagnosed postnatally and are often the reason these boys had a chromosomal evaluation (Bardsley *et al.*, 2013). Since the discovery of the 47,XYX karyotype, many early studies have focused on the relationship between a 47,XYX karyotype, aggressiveness, and behavioural disturbances —attempting to associate this syndrome with a characteristic profile. However, these studies are not scientifically sound due to selection bias and small samples. Additionally, 90% of the boys with 47,XYX are unidentified, therefore, the developmental and behavioural profile of these boys is largely unknown and requires further investigation.

Neuropsychological and neurological characteristics

47,XYX syndrome is usually associated with a normal IQ. However, verbal IQ may be more affected than performance IQ. There is an increased incidence of reading disorders in boys in 47,XYX which is highly associated with early speech delay.

Many boys require speech therapy in their early years, as they exhibit a speech delay. The incidence of learning disabilities in boys with 47,XYX are increased, with reading and written language skills particularly affected. Difficulties with attention and impulse control are frequently reported and are characteristic of ADHD.

Voxel-based morphology (VBM) revealed that boys with 47,XYX have altered GM volume in the insular and parietal regions relative to neurotypically developing boys (Lepage *et al.*, 2014). Alterations in gray matter volume may account for the reduced motor coordination typically seen in 47,XYX boys. VBM also

found extensive white matter modifications bilaterally in the frontal and superior parietal lobes in 47,XYX boys (Lepage *et al.*, 2014). These white matter differences in the frontal and superior parietal lobes parallel a high prevalence of language-based learning difficulties (specifically dyslexia), spatial orientation deficits, and graphomotor dysfunction/dysgraphia characterized in the 47,XYX profile.

White matter volumes are typically larger in the frontotemporal region of the brain, which allows for efficient brain signaling and coordination between visual memories, language comprehension, and emotional association systems. Insular and frontotemporal grey and white matter is reduced in males with 47,XYX, specifically in known language areas (Bryant *et al.*, 2012). These patterns are distinctive and distinguishable from neuroanatomical patterns in typically developing boys and those with 47,XXY (KS). The patterns of regional grey matter and white matter variation in 47,XYX boys are associated with deficits in motor and language abilities (Bryant *et al.*, 2012). These studies further link brain development, behaviour, and developmental outcome in another XY chromosomal disorder and provide a possible mechanistic support that X and Y chromosomes may differentially impact brain morphology.

47,XYX syndrome is associated with higher risk for seizures, focal epilepsy, and an electroclinical pattern characterized by focal spike and waves (similar to benign focal epilepsy) (Torniero, 2010). Males with 47,XYX show increased total grey matter and white matter volume when compared to 46,XY and 47,XXY (KS) males (Bryant, 2012). Increased grey matter may be the result of reduced synaptic pruning, leading to altered synaptic function and possible increased seizure risk (Bardsley, 2013).

Available guidelines of behavioural assessment/treatment/management

Once 47,XYX has been diagnosed, a comprehensive neurodevelopmental evaluation is important for the management of this syndrome (Samango-Sprouse & Gropman, 2016). Occupational and physical therapy may be recommended for infants and young boys who have low muscle tone (hypotonia), and speech therapy may be needed for boys who have speech

delay. Speech therapy should focus on eliminating the underlying oral motor weakness and dysfunction through a targeted approach. In the school setting, assistance from special educators or individualised education programs (IEPs) will be helpful to address challenges with executive dysfunction, reading disorders, ADHD, or other disabilities.

Behavioural therapy or medication for boys may be prescribed for 47,XYX boys with ADHD and/or behavioural problems. In some cases, acne treatment may be beneficial in boosting self-confidence. Hormonal therapy may be also recommended to supplement development and growth.

Useful websites/associations for more information

- The Association for X and Y Chromosome Variations (AXYS)
<https://genetic.org/variations/about-xyx/>
- The Focus Foundation
<http://thefocusfoundation.org/x-y-chromosomal-variations/xyx/>
- Genetics Home Reference
<https://ghr.nlm.nih.gov/condition/47xyx-syndrome>
- Genetic and Rare Diseases (GARD) Information Center
https://rarediseases.info.nih.gov/diseases/5674/47-xyx-syndrome#ref_9860
- National Organization for Rare Disorders (NORD)
<https://rarediseases.org/rare-diseases/xyx-syndrome/>

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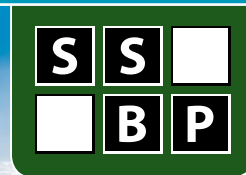
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The 28th SSBP International Research Symposium

Educational Day: 3rd September 2026 • Research Symposium 4th – 5th September 2026 • Edinburgh, UK

Translational Synergies: Bridging Fundamental Science and Clinical Research in Genetic Neurodevelopmental Conditions

The Society for the Study of Behavioural Phenotypes will be holding their 28th International Research Symposium in Edinburgh, UK on the 4th and 5th September 2025. The Educational Day will be held on 3rd September. The theme will be: Translational Synergies: Bridging Fundamental Science and Clinical Research in Genetic Neurodevelopmental Conditions

We look forward to welcoming you to Edinburgh, the historic capital of Scotland. Famous for its International Arts Festival, Edinburgh offers a rich mix of culture and history, from the iconic Castle and Royal Yacht Britannia to the UNESCO World Heritage listed architecture of its Old and New Towns. It also serves as an ideal gateway to explore the many other attractions of Scotland.

Abstract submission opens: **March 2026**

Deadline for abstract submission: **15th May 2026**

Registration opens: **May 2026**

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