25th SSBP International Research Symposium

Programme Book

14th – 15th September 2023 • Virtual Symposium

Save the date!

26th SSBP International Research Symposium will be held in Bali, Indonesia 5th–7th September 2024

Abstract submission opens: March 2024
Registration opens: April 2024
Deadline for online abstract submission: 15th May 2024
Deadline for discounted earlybird registration: 26th July 2024

Educational Day: 5th September 2024
Research Symposium: 6th–7th 2024

Join us in Bali, Indonesia for our 26th research symposium. The theme will be:
Early identification and treatment of genetic and neurodevelopmental disorders

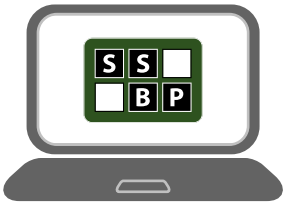
See **www.ssbp.org.uk** for further information
and details on how to submit an abstract for an oral or poster presentation

The Society for the Study
of Behavioural Phenotypes

14th–15th September 2023

The 25th SSBP International Research Symposium

Virtual Symposium



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Welcome from the Conference Organisers

We would really like to welcome you all from across the world to our second online conference of the Society for the Study of Behavioural Phenotypes. It continues to be difficult and challenging times for many of us in the world of Academic research, but we would especially like to pay tribute to the children, families and individuals who are the reason we do what we do and particularly acknowledge the valuable contribution they make to the understanding of not only their own challenges but also the broader community.

In the current era of readily available technology there are challenges to be able to adapt and utilise these advances for the benefits of society and people with disabilities but also make sure that no one is left behind. We are particularly delighted to welcome those people from low and middle income countries who we recognise can find it harder to travel to International meetings (and indeed the economics of flying at present make this challenging for many) but we are delighted that this year's online format can be more accessible for all.

The Society does benefit greatly from the face-to-face gathering and exchange of ideas, and with this in mind we are really looking forward to gathering in Indonesia- Bali next year.

We are however really delighted to present across 4 sessions a combination of excellent invited speakers and research presentations from across the globe reflecting a variety of research being undertaken in the field of Behavioural phenotypes.

There will be 4 sessions at times largely relating to presenter timezones, each consisting of blocks with an invited speaker followed by a number of shorter presentations and a live online question session. There will also be two poster sessions but please take the opportunity to use the website and the Poster Gallery in Gather to explore the posters when you can. Access to the presentations will be present for 30 days after the conference. There are number of awards which will be presented during the meeting so check your program for these.

Welcome and we hope you enjoy the meeting! We hope to see you at each of the sessions you can get to, and please catch up afterwards on anything you missed!

Honey Heussler, Randi Hagerman, Petrus de Vries, Johan Lundin Kleberg
Conference Coordinators

Virtual Conference Organisers

Associate Professor Honey Heussler

Dr Honey Heussler is a Developmental/ Behavioural Paediatrician and Sleep Physician. She is an Associate Professor with the University of Queensland and is Medical Director, Child Development Services as well as clinical responsibility in Behavioural and Sleep clinics with Children's Health Queensland. She is also Co- director of the Centre for Clinical Trials in Rare Neurodevelopmental Disorders at the Queensland Children's Hospital.

Professor Randi Hagerman

Dr. Randi Hagerman is a developmental and behavioral pediatrician, a Distinguished Professor of Pediatrics and the Medical Director of the MIND Institute at UC Davis. She is internationally recognized as both a clinician and researcher in the field of neurodevelopmental disorders including autism and fragile X syndrome. Dr. Hagerman received her M.D. from Stanford University, where she also carried out her Pediatric residency. She completed a Fellowship in Learning and Disabilities and Ambulatory Pediatrics at UC San Diego, then led Developmental and Behavioral Pediatrics at the University of Colorado for 20 years. She co-founded the National Fragile X Foundation in 1984. In 2000, Hagerman joined the MIND Institute and she carries out treatment trials for Fragile X syndrome, ASD and FXTAS. There, she and her team discovered the Fragile X-associated Tremor/Ataxia Syndrome (FXTAS), a neurodegenerative disorder associated with the fragile X premutation.

Professor Petrus de Vries

Petrus de Vries is the Professor of Child & Adolescent Psychiatry and Founding Director of the Centre for Autism Research in Africa (CARA) at the University of Cape Town. He trained in Medicine at Stellenbosch University in South Africa before moving to the UK where he completed his clinical training in Psychiatry and Child & Adolescent Psychiatry, and a PhD in Developmental Neuroscience at the University of Cambridge. He returned to South Africa in 2012. He has a longstanding clinical research programme in Tuberous Sclerosis Complex (TSC) and its associated neuropsychiatric disorders (TAND) and currently co-leads the TANDem project with Prof Anna Jansen from Belgium. He joined the SSBP in 1998 and has been a member of the SSBP Executive Committee since 2003. He was Treasurer from 2007-2008 and Chairman from 2008-2017.

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Associate Professor Johan Lundin Kleberg

Johan Lundin Kleberg is an associate professor at the department of psychology, Stockholm university, and a researcher at the Rare Diseases research group at the Karolinska institute. Dr. Kleberg uses experimental methods such as eye tracking and pupillometry and computational modeling to study reward processing, social attention, and decision making in atypical development. He is currently conducting studies of Williams syndrome, Turner syndrome, Smith-Magenis syndrome and Coffin-Siris syndrome as well as of child psychiatric conditions such as depression and social anxiety.

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Scientific Committee

A/Prof Honey Heussler (Chair)
Medical Director,
Child Development at the Lady Cilento Children's Hospital, Children's Health Queensland, Australia
Associate Professor,
Mater Research Institute and Centre for Children's Health Research, University of Queensland, Brisbane, Australia

Professor Randi J. Hagerman
Distinguished Professor of Pediatrics,
University of California Davis in Sacramento
Medical Director,
MIND Institute

Professor Petrus J de Vries
Struengmann Professor of Child & Adolescent Psychiatry,
University of Cape Town, South Africa

A/Prof Johan Lundin Kleberg
Centre for Psychiatry Research,
Department of Clinical Neuroscience, Karolinska Institutet
Associate Professor in Psychology,
Stockholm University

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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

Meetings of the SSBP

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

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

Forthcoming Meetings of the SSBP

2024	Bali, Indonesia	26th International

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The SSBP Executive Committee

Life President	*Dr Martin* ***Bax*** (London)
President	*Professor Patricia* ***Howlin*** (UK) (patricia.howlin@kcl.ac.uk)
Chair	*Prof Honey* ***Heussler*** (Australia) (h.heussler@health.qld.gov.au)
Hon. Secretary	*Professor Anna* ***Jansen*** (Belgium) (Anna.jansen@uzbrussel.be)
Hon. Treasurer	*Dr Heather* ***Windram*** (UK) (hfw30@cam.ac.uk)

Committee	*Dr Kristin Anderson* ***Bakke*** (Norway) (kristinb@ous-hf.no)
	Professor Petrus ***de Vries*** (South Africa) (petrus.devries@uct.ac.za)
	Professor Randi ***Hagerman*** (USA) (randi.hagerman@ucdmc.ucdavis.edu)
	Dr Laura ***Roche*** (Australia) (Laura.roche@newcastle.edu.au)
	D Jane ***Waite*** (UK) (j.waite@aston.ac.uk)
	Dr Kate ***Woodcock*** (UK) (K.A.Woodcock@bham.ac.uk)

Committee: International Representatives

Africa – *Petrus* ***de Vries*** (Cape Town) (petrus.devries@uct.ac.za)

Australia – *Stewart* ***Einfeld*** (Camperdown) (s.einfeld@usyd.edu.au)

Europe – *Kristin* ***Bakke*** (Oslo) (kristinb@ous-hf.no)

USA (West Coast) – *Randi* ***Hagerman*** (Sacramento) (randi.hagerman@ucdmc.ucdavis.edu)

Global – *Pat* ***Howlin*** (London) (patricia.howlin@kcl.ac.uk)

Administrator	*Elizabeth* ***Walmsley*** (ssbpliz@gmail.com)
Conference Administrator	*Rebecca* ***Windram*** (conference@ssbp.org.uk)

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

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

2023 Tom Oppé Distinguished Lecturer: Professor Mustafa Sahin

Mustafa Sahin, M.D., Ph.D., is Professor of Neurology at Harvard Medical School and Director the Rosamund Stone Zander Translational Neuroscience Center at BCH. He has established and directs and the Multidisciplinary Tuberous Sclerosis Program at Boston Children's Hospital. The research in the Sahin laboratory is directed at understanding the cellular mechanisms of neuronal connectivity and their relationship to neurological dysfunction. His research focuses on tuberous sclerosis complex (TSC) and related neurodevelopmental disorders using cell and animal model as well as clinical investigations. He is the PI of a Rare Diseases Clinical Research Network (RDCRN) studying the comparative pathobiology of TSC, PTEN and SHANK3 mutations in patients as well as co-PI of the BCH/HMS Intellectual and Developmental Disorders Research Center (IDDRC).

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Patricia Howlin and the Patricia Howlin Prize Lecture

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 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 £100 (or equivalent) and an award certificate - both of which will be presented to the winner during the SSBP Research symposium.

Patricia Howlin Lecturers

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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2023 Pat Howlin Lecturer: Dr Laura Roche

Laura Roche received her Ph.D. in Educational Psychology from Victoria University in Wellington, New Zealand. She is currently a lecturer in Special and Inclusive Education at the University of Newcastle in Newcastle, NSW Australia. Laura teaches in the areas of neurodevelopment and early childhood education for pre-school aged children with disabilities. Her research focuses on social-communication intervention for individuals with developmental disabilities and for those diagnosed with rare genetic syndromes. Laura has co-authored numerous journal articles and book chapters describing applied behavioural intervention studies for supporting adaptive skills for those with developmental disabilities and rare genetic syndromes.

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.

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 £100 (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

2023	Jeanne Wolstencroft
2022	The TAND Consortium
2019	Ms Siobhan Blackwell

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2023 Leclezio-de Vries Lecturer: Dr Jeanne Wolstencroft

Dr Jeanne Wolstencroft is a Research Fellow based at the Great Ormond Street Institute of Child Health at UCL. Her main research interests are understanding the impact of co-occurring mental health difficulties in children and young people with neurodevelopmental disorders and/or rare genetic disorders and digital approaches to psycho-social intervention for these children and young people.

Jeanne is currently investigating changes in the mental health and behaviour of children with rare genetic disorders in the national IMAGINE ID study (Intellectual Disability and Mental Health: Assessing the Genomic Impact on Neurodevelopment). Jeanne is a co-investigator on the Children's Autism Technology Assisted Assessments (CHATA) project which aims to digitise autism assessment procedures for families from diverse ethnic backgrounds. She has also received a Child Mental Health Research Strategic Grant to co-produce a digital mental health intervention for children with rare genetic disorders and irritability.
https://iris.ucl.ac.uk/iris/browse/profile?upi=JWOLS89

Other SSBP Prizes and Awards

The James Harris Scholarship

The James Harris Scholarship will be awarded for the first time in 2023. This award is given in memory of James, a longstanding member of the SSBP executive committee The James Harris Scholarship supports a delegate from a Low or Middle Income Country to attend the SSBP conference and present their work.

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.

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E-Venues

SSBP Website
www.ssbp.org.uk

The SSBP Website is the central base for the conference.

How to access: You will receive individual login details by email to access the conference area of the website. Please add conference@ssbp.org.uk to your contacts to make sure that you receive this information

From the home page, you can access all conference content, and you can view a live-stream of the presentations.

- **All video presentations are also available for 'catch-up' viewing from the website**, and we will endeavour to upload recordings of the live discussion sessions.
- **Poster presentations will be made available on the website after the two live poster sessions**. Please do come along to poster sessions A and B to browse the posters and to discuss with the authors.
- **Comment boxes will be next to each presentation**, and you can use these to post public questions to authors.
- The entire Conference Website area will be available for 30 days after the end of the conference.

Zoom
zoom.us

All live discussions, Round Tables and Q/A will be hosted on Zoom.

How to access: Links to the zoom calls will be available in the *Conference Website home page* area.

Please join the Zoom calls a few minutes before the start of the session.

If possible, please check that your screen name matches the name used in your registration.

Asking Questions

During the Zoom discussions, you can ask questions in two ways:

- **'Raise your Hand'** to request to speak (In the menu bar at the bottom of the screen, click on Raise Hand. (You can click this button again to Lower Hand.)
- **Type a message into the chat.** (In the menu bar, click on Chat and message to everyone.)

Questions that have been posted on the website may also be discussed in the Zoom Q/A, so if you can't make the session, please do post any questions on the website before the live session.

Gather
www.gather.town

The two Live Poster Sessions will be hosted on Gather.

How to access:
Links to the SSBP Gather space will be available on the Conference Website Home Page.

SSBP Gather Guide: https://ssbp.org.uk/wp-content/uploads/2023/09/SSBP-Guide-to-Gather-2023.pdf

Gather is a virtual conference space, which runs in your internet browser. You can move an avatar around the space, view posters on posterboards and discuss with other attendees in real-time video chat.

Poster authors will be available to discuss their posters in one of the two live poster sessions, depending on their timezone.

Gather will be open all day throughout the conference, so please do feel free to use the space as a place to drop in, and to meet and chat.

Gather is simple to use, but does take a few minutes to set up the first time you use it. We recommend that you follow **the SSBP Gather Guide, and either test out Gather before the first session, or allow an extra 10 minutes to get started**.

You will need to use a computer rather than a mobile device for the best experience.

Keynote Speaker Profiles:

(in order of presentation)

Professor Jo Van Herwegen

Jo Van Herwegen is a professor in Developmental Psychology and Education at Institute of Education, UCL's faculty for Education and Society, and director of the Child Development and Learning Difficulties lab. Her research focuses on improving educational outcomes for those with learning difficulties and neurodevelopmental disorders, using evidence from developmental psychology and educational neuroscience. Jo has co-edited two books and has written over 60 peer-reviewed articles and book chapters. Her research has been funded by a number of charities and research councils, including EEF, Nuffield Foundation, UKRI and ESRC. Her research has included both national and international studies focusing on intervention evaluations of mathematical programmes for those with SEND, evaluation of the SEND code of practice and EHCPs, issues and best practice around school transitions for those with SEND and CPD for educational staff as well as neuromyths related to those with SEND and impact of COVID19 for those with SEND.

She is currently Head of Research for the department of Psychology and Human Development and member of the executive committee for the European Association for Research on Learning and Instruction (EARLI).

https://iris.ucl.ac.uk/iris/browse/profile?upi=VANHE52

Twitter @JoVanHerwegen

Professor Dawn Adams

Professor Dawn Adams is the Director of the Autism Centre of Excellence, Griffith University. As well as being an academic, she is also a Clinical Psychologist. She has published over 75 research articles and been awarded AUD$4.75 million in research funding.

Dawn uses both her clinical and research experience to inform her work in the area of anxiety, mental health and wellbeing in autistic individuals. Her work in this area has led her to co-develop and evaluating an autism-specific anxiety prevention/intervention for autistic preschoolers and led work on identifying the challenges autistic people face when accessing mental health services in Australia. To ensure her work is driven by, and has immediate relevance to, the autistic and autism communities, all of Dawn's current research grants and projects are collaborations with community and/or clinical partners.

Dr Giacomo Vivanti

Giacomo Vivanti, PhD, is an Associate Professor at the A.J. Drexel Autism Institute, Drexel University, Philadelphia, USA, where he is the leader of the Early Detection and Intervention program. Additionally, he is an Honorary Research Fellow at the Olga Tennison Autism Research Centre at La Trobe University, Melbourne, and an Associate Editor of the Journal of Autism and Developmental Disorders. His research focuses on early learning processes and early intervention strategies for autism and other neurodevelopmental conditions. Dr Vivanti has presented at more than 100 national and international conferences on topics related to neurodevelopmental disorders, and he is the author of over 100 peer-reviewed scientific articles, chapters and books. He is consultant for clinical, research, and policy organizations related to autism in the US, Europe and Australia, including the US Department of Defense Autism Research Program and the US National Institute of Health.

Professor Bruno Falissard

After some initial training in mathematics and fundamental physics (Ecole Polytechnique, Paris), Bruno Falissard engaged in medical studies and specialized in Child and Adolescent Psychiatry in 1991. His PhD was in biostatistics and his post doc in psychometrics and exploratory multimensional methods. He was assistant professor in child and adolescent psychiatry in 1996-1997, associate professor in Public Health in 1997-2002 and full professor in Public health from 2002. He is at the head of the "Center of Epidemiology and Population Health" (600 members). He is co-author of many papers and books. He has a clinical activity in child and adolescent psychiatry. His personal areas of research are about methodology and epistemology of mental health research. In 2015 he became president of IACAPAP (International Association of Child and Adolescent Psychiatry and Allied Professions, the term ended in 2018) and member of the French Academy of Medicine. He was awarded the Ülkü Ülgür International Scholar Award by the American Academy of Child and Adolescent Psychiatry in 2019.

Professor Walter Kaufmann

Dr. Walter Kaufmann is currently the Chief Scientific Officer for Anavex Life Sciences Corp. and an Adjunct Professor of Human Genetics at Emory University. He has over 25 years of clinical research experience in neurodevelopmental disorders, with emphasis on Rett syndrome and fragile X syndrome, during a career that has included full professorship at the medical schools of Johns Hopkins University and Harvard University. He has committed himself to laboratory investigations of molecular pathways, neuroimaging, animal models of disease, and clinical trials of targeted, disease-modifying therapies. His work helped to define Rett syndrome as a disorder of synaptogenesis, leading to a better understanding of its underlying mechanisms.

Dr. Kaufmann has also held several leadership positions, including advisor and reviewer to CDKL5, FOXG1, Rett syndrome, and fragile X syndrome advocacy groups. He is a member of the Scientific and Clinical Advisory Committee of the National Fragile X Foundation. Other positions he has held include Chair of the International Consortium on Rett Syndrome Clinical Researchers (RettSearch) and member of DSM-5's Neurodevelopmental Disorders Work Group, which developed the current diagnostic guidelines for intellectual disability and autism spectrum disorder. He has also served as member and chair of NIH and DoD (CDMRP) study sections reviewing grants on neurodevelopmental and other neurological disorders. He is also the Editor of the first book on clinical aspects of Rett syndrome (Mac Keith Press), section Editor for Pediatric Neurology for Current Neurology and Neuroscience Reports, and a member of the editorial board of the journals Brain Sciences and Frontiers (Epigenomics & Epigenetics).

Research Symposium Programme

All times are given here in UK BST (UTC+1), to see programme in a range of time zones, please go to ssbp.org.uk
E-venues: For further information about how to access the e-venues please see page 19.

Session 1 - Thursday 14th September

Time (UK BST)		Session 1	E-Venue
08:00 - 08:30		**KEYNOTE: 1. Jo Van Herwegen** - Improving Educational Outcomes for Young People with Williams Syndrome: From Theory to Practice (and Back Again)	*Website*
08:30 - 09:00		**Free Communications** - 3 x 10 minutes **2. Jente Verbesselt** - Clinical features and developmental trajectories in school-aged children with 16p11.2 deletion **3. Catherine Franklin** - Down Syndrome Regression Disorder **4. Elizabeth Elliott** - The Face of Fetal Alcohol Spectrum Disorder in Australia	*Website*
09:00 - 09:05	**LIVE**	**Welcome from the Organising Committee**	*Zoom*
09:05 - 09:35	**LIVE**	**Q/A Discussion** (Chair: Honey Heussler) - Van Herwegen, Verbesselt, Franklin, Elliott	*Zoom*
09:35 - 09:50		**BREAK** - 15 min	
09:50 - 10:20		**KEYNOTE: 5. Dawn Adams** - Understanding Mental Health and Well-Being in the Context of Neurodiversity	*Website*
10:20 - 10:40		**Free Communications** - 2 x 10 minutes **6. Jessica Hughes** - A parent-led intervention to reduce anxiety in autistic children with severe to profound intellectual disabilities: current data from the LADDERS proof-of-concept study **7. Mirthe Klein Haneveld** - Improving guidelines for individuals with rare genetic neurodevelopmental disorders: a systematic review and critical appraisal of existing guidelines	*Website*
10:40 - 11:05	**LIVE**	**Q/A Discussion** (Chair: Jane Waite) - Adams, Hughes, Klein Haneveld	*Zoom*
11:05 - 11:20		**BREAK** - 15 min	
11:20 - 11:35		**THE PAT HOWLIN LECTURE: 8. Laura Roche** - Enhancing Expressive Communication Using AAC: A Case Study of One Boy with 22q11.2 Deletion Syndrome	*Website*
11:35 - 11:40	**LIVE**	**Q/A Discussion** (Chair: Pat Howlin) - Roche	*Zoom*
11:40 - 12:00	**LIVE**	**Q/A Discussion** (Chair: Pat Howlin) - Why is it so difficult to do intervention research involving individuals with genetic conditions?	*Zoom*

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Session 2 - Thursday 14th September (Friday 15th September in Australia)

Time (UK BST)		Session 2	E-Venue
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17:30 - 18:00		**Free Communications** - 3 x 10 minutes	*Website*
		10. Nola Chambers - Development of consensus recommendations for the identification and treatment of TSC-Associated Neuropsychiatric Disorders (TAND)	
		11. Agnies van Eeghen - Behavioural outcomes of treatment with cannabidiol oral solution in individuals with seizures associated with tuberous sclerosis complex: design of an ongoing phase 4 trial (EpiCom)	
		12. Nadja Bednarczuk - Behavioural and developmental characteristics of SYNGAP1-related intellectual disability	
18:00 - 18:05	**LIVE**	**Welcome from the Organising Committee**	*Zoom*
18:05 - 18:35	**LIVE**	**Q/A Discussion** (Chair: Anna Jansen) - Sahin, Chambers, van Eeghen, Bednarczuk	*Zoom*
18:35 - 18:50		**BREAK** - 15 min	
18:50 - 19:35		**KEYNOTE: 13. Giacomo Vivanti** - Phenotypic Overlap Between Autism, Williams Syndrome and Angelman Syndrome	*Website*
19:35 - 20:05		**Free Communications** - 3 x 10 minutes	*Website*
		14. Tally Tafla - Critical items of CBCLs in a Brazilian sample of Williams and Down syndrome individuals	
		15. Nicole Tartaglia - The eXtraordinarY Babies Study: Utilization of Early Intervention Therapies in 289 Children with a Prenatal Diagnosis of Sex Chromosome Aneuploidy (XXY, XYY, Trisomy X) and Relationship of Speech Therapy to Speech-Language Outcomes at 36 months of age	
		16. Talia Thompson - Anxiety in Turner syndrome: Engaging community to address barriers and facilitators to diagnosis and care	
20:05 - 20:15		**BREAK** - 15 min	
20:15 - 20:45	**LIVE**	**Q/A Discussion** (Chair: Randi Hagerman) - Vivanti, Tafla, Tartaglia, Thompson	*Zoom*
20:45		**Virtual Social** - Coffee and a chance to chat	*Gather*

Session 3 - Friday 15th September

Time (UK BST)		Session 2	E-Venue
08:00 - 08:45	**LIVE**	**Poster Session A** Presentation of posters, plus poster browsing time. (Chair: Johan Lundin Kleberg)	*Gather*
08:45 - 09:00		**BREAK** - 15 min	
09:00 - 09:30		**KEYNOTE: 17. Bruno Falissard** - Did We Take the Right Train in Promoting the Concept of 'Neurodevelopmental Disorders'?	*Website*
09:30 - 10:00		**Free Communications** - 3 x 10 minutes **18. Honey Heussler** - An Open-Label Trial Assessing Short- and Long-Term Tolerability and Efficacy of ZYN002 (Cannabidiol) Administered as a Transdermal Gel to Children and Adolescents with 22q11.2 Deletion Syndrome (INSPIRE) **19. Nadia van Silfhout** - PROM4RARE: Giving a voice to individuals with rare genetic neurodevelopmental disorders **20. Lauren Shelley** - Associations between executive functioning, intolerance of uncertainty and behaviours that challenge in SATB2-associated syndrome	*Website*
10:00 - 10:30	**LIVE**	**Q/A Discussion** (Chair: Honey Heussler) - Falissard, Heussler, van Silfhout, Shelley	*Zoom*
10:30 - 10:45		**BREAK** - 15 min	
10:45 - 11:00	**LIVE**	**A Presentation Introducing SSBP 2024 - Indonesia**	*Zoom*
11:00 - 12:00	**LIVE**	**SSBP AGM**	*Zoom*
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Session 4 - Friday 15th September (Saturday 16th September in Australia)

Time (UK BST)		Session 2	E-Venue
17:00 - 17:45	**LIVE**	**Poster Session B** Presentation of posters, plus poster browsing time (Chair: Randi Hagerman)	*Gather*
17:45 - 18:00		**BREAK** - 15 min	
18:00 - 18:15	**LIVE**	**THE LECLEZIO-DE VRIES LECTURE:** 21. Jeanne Wolstencroft - Autism Picture Tool: Children and young people's views on consent	*Website*
18:15 - 18:20	**LIVE**	**Q/A Discussion** (Chair: Petrus de Vries) - Wolstencroft	*Zoom*
18:20 - 18:50	**LIVE**	**Panel Discussion** (Chair: Petrus de Vries) - Towards socially responsive and participatory research around the globe	*Zoom*
18:50 - 19:05		**BREAK** - 15 min	
19:05 - 19:35		**KEYNOTE:** 22. Walter Kaufmann - Development of Targeted Treatments for Rett Syndrome	*Website*
19:35 - 20:15		**Free Communications** - 4 x 10 minutes 23. Randi Hagerman - Open Label Trial of Sulforaphane in FXTAS 24. Dejan Budimirovic - High frequency of neuropsychiatric disorders and a need for treatment in patients with FXAND linked to FMR1 gene premutation carriers 25. Federica Alice Maria Montanaro - Fragile X Syndrome and FMR1 premutation: results from a survey on associated conditions and treatment priorities in Italy 26. Kayla Smith - The Relationship between Autism Characteristics, Intolerance of Uncertainty, and Anxiety in Fragile X Syndrome	*Website*
20:15 - 20:20		**SHORT BREAK** - 5 min	
20:20 - 20:55	**LIVE**	**Q/A Discussion** (Chair: Randi Hagerman) - Kaufmann, Hagerman, Budimirovic, Montanaro, Smith	*Zoom*
20:55 - 21:00		**Thanks and Goodbyes**	*Zoom*

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Abstracts for Research Symposium 14th – 15th September *(in order of presentation)*

1. KEYNOTE: Improving Educational Outcomes for Young People with Williams Syndrome: From Theory to Practice (and Back Again)

Van Herwegen J.[1]

[1] *UCL Institute of Education, UK*

Williams syndrome (WS) is a rare genetic syndrome (1 in 18,000 life births) that results in an uneven cognitive profile and intellectual disabilities, in addition to a specific behavioural and physical profile. This profile of complex needs may make it challenging to support children with WS in schools and many individuals with WS have poor educational outcomes. In this talk I will discuss what we have learned about WS through a multi-lab collaboration to build a large cross-sectional and longitudinal database on cognitive development in WS (WiSDom) as well as research that has examined the issues related to educational provision for individuals with WS. I will present how we have co-created two sets of educational guidelines with teachers as well as young individuals with WS themselves and what the theoretical implications of this process has been. Finally, I will highlight future research priorities to raise educational outcomes in individuals with WS (and other neurodevelopmental conditions.

Keywords: SEN, Williams syndrome, mathematics, education, educational outcomes

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2. Clinical Features and Developmental Trajectories in School-Aged Children with 16p11.2 Deletion

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

[1] Department of Human genetics, KU Leuven, Belgium

[2] Department of Neurosciences, Research Group Experimental Oto-Rhino-Laryngology (ExpORL), KU Leuven, Belgium

[3] Department of Oto-Rhino-Laryngology, Head & Neck Surgery, MUCLA, University Hospitals Leuven, Campus Gasthuisberg, Belgium

[4] Centre for Human Genetics, University Hospitals Leuven, Belgium

Background: 16p11.2 deletion syndrome (16p11.2 DS, BP4-BP5) is a recurrent CNV that occurs *de novo* in approximately 70% of cases and confers risk for neurodevelopmental disorders (NDD), including intellectual disability (ID) and autism spectrum disorders (ASD). This study focusses on presenting symptoms, developmental milestones and cognitive trajectories.

Methods: Digital medical records, in-person assessments and parental interviews on medical and developmental history of 23 children (5-16 years, 12/16 *de novo*) with a confirmed BP4-BP5 16p11.2 DS diagnosed and followed up at the Center for Human Genetics UZ Leuven were reviewed and analysed. Standardised intelligence tests (WISC-V NL) were administered in all, and longitudinal IQ-data were available in a subgroup (83%,19/23).

Results: Most prominent clinical issues were nutritional problems (68%,15/22), transient or permanent hearing impairment (52%,12/23), overweight (50%,10/20) and epilepsy or seizures (43%,10/23). Developmental milestones were delayed across several developmental domains (motor, language). At least one neurodevelopmental disorder (NDD) was diagnosed in 74% (17/23), most commonly ASD (48%, 11/23) and developmental coordination disorder (DCD: 36%, 8/23). Average IQ was in the mild ID range (IQ 69.2; SD: 12.7; range 45-91) with 39% having borderline IQ (IQ 70-84). Longitudinal IQ-data with first assessment at a median age of 5y10m and second timepoint at a median age of 10y10m, indicate that children with 16p11.2 DS perform statistically significantly lower on the second timepoint ($p<0.001$) with 53% (10/19) showing a growing into deficit trajectory.

Conclusion: Delayed motor and language milestones are frequent in 16p11.2 DS carriers (BP4-BP5), as well as medical issues such as feeding problems, overweight and epilepsy. School-aged children with 16p11.2 DS show increasing learning and cognitive impairments over time and present with high rates of NDD (ASD, DCD). Future studies in larger cohorts including carrier relatives are needed to gain more insight into the penetrance and phenotypic variability of 16p11.2 DS.

Keywords: 16p11.2 deletion syndrome, copy number variants, early development, developmental trajectories, deep phenotyping

3. Down Syndrome Regression Disorder

***Franklin C.S.*[1,2]**

[1] *Queensland Centre for Intellectual and Developmental Disability, Mater Research Institute-UQ, The University of Queensland, Australia*

[2] *Mater Intellectual Disability and Autism Service, Mater Hospital South Brisbane, Australia*

Background: Down Syndrome Regression Disorder (DSRD) is a disorder associated with acute and unexplained regression in adolescents and young adults with Down syndrome. The regression includes a decline in speech, social withdrawal and functional decline, and is usually accompanied by catatonia.

Methods: This presentation will review the current literature, in relation to theories of aetiology, recently defined consensus diagnostic criteria, suggested investigations and treatments.

Results: DSRD is a devastating condition and if unrecognised and untreated is also disabling. It was first described in the early 1900's, but interest has grown in recent years, to the point where patterns of common presentation and psychiatric and immunologic treatments have been described. The gaps in the current knowledge base and the various barriers to access to healthcare experienced by people with this condition will also be described.

Conclusion: The clinical presentation of DSRD, including catatonia and its other clinical manifestations have been defined. There is emerging evidence to support a variety of treatments, including treatments for catatonia and intravenous immunogloubulin. Further research into prevalence, biomarkers and effective treatments is needed.

Keywords: Down syndrome, regression, catatonia

4. The Face of Fetal Alcohol Spectrum Disorder in Australia

***Elliott E.J.*[1,2 3], *Zimmet M.*[1,3,4], *Tsang T.* [1,3]**

[1] *University of Sydney, Australia*

[2] *Sydney Children's Hospitals Network, Westmead, Australia*

[3] *Australian Paediatric Surveillance Unit, Australia*

[4] *Royal Far West, Australia*

Background: Over 60% Australian women report alcohol use in pregnancy and FASD is recognised as an adverse consequence. We aimed to describe the epidemiology of FASD in Australia.

Methods: National prospective surveillance for FASD using the Australian Paediatric Surveillance Unit. Monthly reporting by ~1500 paediatricians (January 2015-30 Dec 2022). Reported data include demographics, physical and behavioural phenotype, neurodevelopmental profile and service use of newly diagnosed cases. Cases were classified using criteria in the Australian Guide to the Diagnosis of FASD and included in the FASD Australian Registry (FASDAR).

Results: Of 1359 notified cases, 1011 were confirmed after excluding duplicates/ineligible cases (incidence 2.7/105 <15 years/annum) and rate increased over time ($p<0.0001$). Mean age at diagnosis was 8.5y (1-14.9y), 67% were boys, 55% Aboriginal and/or Torres Strait Islander, 19% had a sibling with FASD. Most came from Western Australia (28%), Queensland (24%) and NSW (23%), 21% from remote/very remote regions. Only 22% lived with a biological parent, 74% had child protection contact, and prenatal alcohol exposure (PAE) was high risk in 89%. Most (80%) were diagnosed in a multi-disciplinary FASD assessment clinic; all diagnoses involved a paediatrician.

Only 17% had all 3 sentinel facial features (small palpebral fissure length, flat philtrum, thin upper lip), 18% had microcephaly, 17% had major (brain, heart) or minor (clinodactyly, ptosis, and epicanthic folds) congenital anomalies. All had severe neurodevelopmental impairment in ≥3 domains, commonly attention (80%), executive functioning (76%), adaptive behaviour (72%), and language (66%). Co-morbidities included complex early life trauma, sleep disorder, Autism Spectrum Disorder, anxiety and hearing loss. Chromosome microarray revealed rare copy number variant in 24%, some pathogenic. No child had Fragile-X.

Conclusion: FASDAR provides unique, current, national Australian data on FASD to inform policy and practice. They indicate need for capacity-building in clinicians, screening of high-risk groups and evidence-based prevention strategies.

Keywords: Fetal Alcohol Spectrum Disorder, epidemiology, phenotype

5. KEYNOTE: Understanding Mental Health and Well-Being in the Context of Neurodiversity

***Adams D.*[1]**

[1] *Autism Centre of Excellence (ACE), Griffith University, Australia*

The COVID-19 pandemic has drawn significant attention to people's mental health and well-being and the need for effective and accessible mental health supports. However, even prior to the pandemic, it was recognised that autistic individuals (and individuals with other neurodevelopmental conditions) experience elevated rates of mental health challenges, with few tailored, effective or accessible supports available to them. In this keynote, I shall explore research which aims to identify and understand mental health in the context of neurodiversity, and evaluate which, if any, models, measures or interventions take neurotype into account. As part of this, I will explore evidence for factors which may enhance or prevent a neurodivergent individual experiencing mental health challenges and consider how and why these may differ from those reported within neurotypical individuals. I will close by considering how far the research in this area can inform clinical pathways to improved mental health and wellbeing for neurodivergent individuals now, or in the future.

Keywords: autism, psychology, therapy, disability, anxiety

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6. A Parent-Led Intervention to Reduce Anxiety in Autistic Children with Severe to Profound Intellectual Disabilities: Current Data From the LADDERS Proof-of-Concept Study

*Waite J.[1], Pearson E.[1], **Hughes J.**[1], Tarver J.[1], Edwards G.[1], Bird M.[1], Greenhill C.[1]*

[1] School of Psychology, College of Health and Life Sciences, Aston University, Birmingham, UK

Background: Autistic individuals with severe to profound intellectual disability (ID) are at risk of anxiety. However, there are very few evidence-based interventions aimed at reducing anxiety in this group. Psychological approaches such as graded exposure and emotion regulation have been evidenced as effective in reducing anxiety in other clinical populations. Adaptations and applications of interventions to reduce anxiety in autistic people need to consider the specific profile of behaviour, cognition and emotion associated with autism. LADDERS is a 16-week parent-led intervention accounting for aspects of the behavioural profile associated with autism. This pilot study aims to assess whether LADDERS reduces anxiety and avoidance-related behaviour in autistic children with severe to profound ID.

Methods: The study utilises a multiple baseline, single case experimental design. The primary outcome measure (POM) is parent report of child anxiety completed daily during baseline through to 2-weeks post-LADDERS intervention. Secondary outcome measures (SOM) include a direct observation of child anxiety, teacher anxiety diaries and parent-report questionnaires of child wellbeing. All questionnaire measures were completed pre-intervention, post-intervention (week 16) and at 2-month follow up (week 24).

Results: Six parent-child dyads were eligible to proceed from baseline with a 100% retention rate. Visual inspection of POM data suggests a decrease in reported anxiety for 4 out of 6 participants. Preliminary statistical comparison of pre- and post-intervention POM for participants was conducted using Non-overlap of all Pairs (NAP), which is appropriate for smaller datasets. 4 out of 6 NAP values indicate a medium effect size (range = 0.3-0.81). Analysis of the SOM will further examine the effectiveness of the LADDERS intervention.

Conclusions: Preliminary analysis suggests the LADDERS intervention may reduce anxiety and anxiety-related avoidance in autistic children with severe to profound ID. The strengths and limitations of LADDERS will be discussed along with the next steps for the study.

Keywords: Autism, intellectual disability, intervention, anxiety

7. Improving Guidelines for Individuals with Rare Genetic Neurodevelopmental Disorders: A Systematic Review and Critical Appraisal of Existing Guidelines

***Klein Haneveld M. J.*[1,2]*, Hieltjes I. J.*[3]*, Cornel M. C.*[4]*, ERN ITHACA Guideline Working Group*[2]*, Gaasterland C. M. W.*[1,2,3]*, Van Eeghen A. M.*[1,2,5]

[1] *Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands.*

[2] *European Reference Network on Rare Congenital Malformations and Rare Intellectual Disability (ERN-ITHACA)*

[3] *Kennisinstituut van de Federatie Medisch Specialisten, Utrecht, The Netherlands*

[4] *Department of Human Genetics, Amsterdam UMC location Vrije Universiteit Amsterdam, Amsterdam, The Netherlands*

[5] *Advisium, 's Heeren Loo Zorggroep, Amersfoort, The Netherlands*

Background: Individuals with rare genetic neurodevelopmental disorders are often affected with intellectual disability, psychiatric manifestations, and complex multi-organ comorbidity, necessitating lifelong and multidisciplinary care. Guidelines can offer valuable support in providing evidence-based care for this population, but their development is challenging. Within the European Reference Network on Rare Congenital Malformations and Rare Intellectual Disability ERN-ITHACA, we create guidelines for genetic syndromes and their shared comorbidities, while improving our methodology through evidence reviews and qualitative research involving all stakeholders. Assessment of the nature and quality of existing guidelines is needed to inform future guideline development efforts.

Methods: We systematically searched MEDLINE, EMBASE, and Orphanet for conditions classified as 'rare genetic intellectual disability' (ORPHA:183757) to identify guidelines for rare genetic neurodevelopmental disorders. Methodological quality was assessed using the AGREE (Appraisal of Guidelines, Research, and Evaluation) II tool.

Results: 70 internationally published guidelines, addressing the diagnosis and/or management of 28 conditions, were identified and reviewed. Guidelines generally scored well on the definition of topic and scope, and clarity of recommendations. Most guidelines were developed by multidisciplinary groups. The extent of involvement of paramedical professionals and affected individuals and families varied. The methodological rigour of development was highly variable with limited reporting of literature searches and consensus methods. Reporting of funding sources was inconsistent, and often there was no procedure for managing conflicts of interest. Implementation aspects were given limited attention.

Conclusion: Comprehensive, high-quality guidelines are lacking for many rare neurodevelopmental disorders. Applying rigorous methodology and ensuring applicability are significant challenges in guideline development. This research aims to inform and improve future guideline development processes, contributing to evidence-based care for individuals with rare neurodevelopmental disorders.

Keywords: genetic neurodevelopmental disorders, guidelines, evidence-based care, methodology, rare disease

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8. Enhancing Expressive Communication Using AAC: A Case Study of One Boy with 22q11.2 Deletion Syndrome

Roche L.[1], Sigafoos J.[2], Campbell L.[1]

[1] The University of Newcastle, Australia

[2] Victoria University of Wellington, New Zealand

Background: Differences, delays and difficulties in expressive language are hallmark features of 22q11.2 deletion syndrome (22q11.2DS). Indeed, the majority of young children with 22q11.2DS will present with a speech or language disorder. These children are candidates for augmentative and alternative communication (AAC) to support and enhance their expressive communication skills. Despite this, the literature lacks evidence of AAC intervention for children with 22q11.2DS.

Methods: We conducted a naturalistic ABA multiple baseline design to teach one young boy to request preferred snacks and ask to play with preferred toys using Picture Exchange (PE). The boy could choose from 6 different snack items, and 5 different toy items. Intervention involved a least-to-most prompting hierarchy, systematic instruction and positive verbal and natural reinforcement. The first author implemented sessions as a model for the boy's mother to follow, whereby over 50% of baseline and intervention, and 100% of follow-up sessions were implemented by the mother. All sessions occurred within the family home with familiar snacks and toys.

Results: During baseline in snacks, the boy produced unclear vocalisations and reached and/or pointed to the desired items. After 4 intervention sessions, the boy reached the pre-determined mastery criteria of 80% or more correct independent PE requests over 3 consecutive sessions. He maintained his independent requesting at 100% across 3 subsequent sessions of follow-up. During baseline in the play condition, he produced unclear vocalisations and reached and/or pointed to the desired items. During intervention, he reached mastery criteria in (*yet to be determined*) sessions.

Conclusion: The young boy was able to quickly learn to use the PE system and this system was easily implemented by his mother, within their family home, using familiar stimuli. Children with 22q11.2DS who experience expressive communication difficulties are candidates for AAC and should be able to access AAC to support their communication skills.

Keywords: DiGeorge syndrome, Augmentative and alternative communication, Parent intervention, Naturalistic communication intervention, Single case experimental design

9. KEYNOTE: Collaborative Translational Studies in Rare Neurogenetic Diseases

Sahin M. [1]

[1] *Boston Children's Hospital, Harvard Medical School, Boston, USA*

Rare deleterious variants with large effect sizes offer a unique opportunity to understand the pathophysiology of neurodevelopmental disorders and provide insights into mechanism-based therapies.

For the past two decades, we have focused a rare genetic disorder – Tuberous Sclerosis Complex (TSC). We have taken a multi-pronged approach characterizing this disease with cellular and animal models as well as with detailed prospective clinical studies. Our preclinical studies have indicated that TSC1/2 loss of function results in neuronal connectivity and excitability abnormalities due to mTOR hyperactivation. These results have contributed to clinical biomarker identification and treatment trials in TSC. Now, we are extending our findings from TSC to other genetic disorders which impinge on the mTOR pathway by studying their pathobiology in a comparative manner to accelerate the clinical trial readiness across a number of developmental synaptopathies, leveraging several sites around the United States that phenotype patients collaboratively using standard operating procedures.

Identification of rare genetic variants has changed the landscape of research in this field; however, to translate these discoveries into rational, mechanism-based, safe, and effective treatments for neurodevelopmental disorders will require building and sustained support of networks/consortia that work closely with patient communities and industry partners.

Keywords: autism, tuberous sclerosis, PTEN, Shank3, MRI, EEG, prevention

10. Development of Consensus Recommendations for the Identification and Treatment of TSC-Associated Neuropsychiatric Disorders (TAND)

Chambers N.[1], Heunis T-M.[2], Vanclooster S.[2], de Waele L.[3,4], Jansen A. C.,[2,5,6], de Vries P.J.[1], TAND Consortium

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[2] Mental Health and Wellbeing Research Group, Department of Public Health, Vrije Universiteit Brussel, Brussels, Belgium

[3] Department of Paediatric Neurology, University Hospitals Leuven, Leuven, Belgium

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[5] Department of Pediatrics, Koningin Mathilde Moeder- en Kindcentrum, Antwerp University Hospital, Antwerp, Belgium

[6] Department of Translational Neurosciences, University of Antwerp, Antwerp, Belgium

Background: Tuberous Sclerosis Complex (TSC) is commonly associated with a wide range of TSC-Associated Neuropsychiatric Disorders (TAND) that are often under-identified and under-treated, yet they contribute significantly to the burden of disease. To date, clinical recommendations for the diagnosis and management of TAND have been limited and non-specific. The goal of this study was to develop comprehensive evidence-based clinical practice recommendations for TAND of relevance to the global TSC community.

Methods: This study was carried out by the TAND Consortium, an international, interdisciplinary and participatory consortium of 24 individuals, including TSC family representatives, from all World Health Organization regions as part of the TANDem Project. At the time of this project, no internationally-adopted standard methodology existed for the generation of clinical practice recommendations. We therefore developed our own systematic procedure consisting of 10 discrete steps which included systematic evidence review, generation of summary statements and recommendations, voting, and consensus discussions to generate evidence-informed consensus recommendations for TAND.

Results: This procedure yielded ten core principles applicable to all individuals with TSC, along with cluster-specific recommendations for each of the seven natural TAND clusters identified in the literature (autism-like, dysregulated behaviour, eat/sleep, mood/anxiety, neuropsychological, overactive/impulsive, and scholastic), and a set of 'wraparound' psychosocial cluster recommendations. The overarching recommendation is to 'screen' for TAND at least annually, to 'act' using appropriate next steps for evaluation and treatment, and to 'repeat' the process to ensure early identification and early intervention with the most appropriate biological and behavioural evidence-informed approaches to support individuals with TSC and their families.

Conclusion: The consensus recommendations provide a systematic framework to approach the identification and treatment of TAND for clinical care teams, and families who live with TSC. As a final aim of the TANDem Project, a TAND Toolkit has been developed to promote implementation of the recommendations.

Keywords: Tuberous sclerosis complex, TAND, consensus recommendations

11. Behavioural Outcomes of Treatment with Cannabidiol Oral Solution in Individuals with Seizures Associated with Tuberous Sclerosis Complex: Design of an Ongoing Phase 4 Trial (EpiCom)

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Background: There are limited treatments for tuberous sclerosis complex (TSC)–associated neuropsychiatric disorders (TAND), which affect ~90% of individuals with TSC. Cannabidiol (CBD; Epidiolex/Epidyolex) treatment reduced TSC-associated seizure frequency and improved patients' overall clinical condition in trials. Anecdotal reports in individuals with TSC, and studies in other rare neurogenetic disorders suggest a positive effect on behavioural manifestations such as irritability. EpiCom is a multicentre, open-label, phase 4 study designed in collaboration with patient advisory groups and healthcare professionals to evaluate behavioural outcomes associated with add-on CBD treatment in individuals with TSC-associated seizures.

Methods: Participants (aged 1–65 years) starting CBD treatment for seizures and with moderate/severe behavioural challenges on Caregiver Global Impression of Severity scale are eligible. After screening, participants will receive CBD (up to 25 mg/kg/d based on individual response and tolerability) for 26 weeks. Following this 26-week treatment period, participants will have the option to continue CBD with standard of care for up to 52 weeks. Key behavioural efficacy endpoints include a change from baseline on the Aberrant Behaviour Checklist (including irritability subscale) and the most problematic behaviour on the TAND-Self-Report, Quantified Checklist (TAND-SQ). Changes in executive function, sleep, quality of life, family functioning, seizure outcomes (symptom severity, retention rate, responder rates, seizure-free days) and safety will also be evaluated.

Results: The trial will enrol ~75 participants at ~20 sites across the US, the UK, The Netherlands, Canada, Israel, and Poland.

Conclusions: The EpiCom study will describe changes in neuropsychiatric outcomes in individuals with TSC who experience seizures and are using CBD. This may inform future studies evaluating potential pharmacotherapy for behavioural outcomes in TSC and similar populations.

Keywords: Tuberous sclerosis complex, treatment-resistant seizures, neuropsychiatric disorders, aberrant behaviour, executive functioning, cannabidiol

12. Behavioural and Developmental Characteristics of SYNGAP1-Related Intellectual Disability

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Background: SYNGAP1 is associated with intellectual disability (SYNGAP1-ID), behavioural difficulties, and autism. The neuropsychiatric phenotype of SYNGAP1-ID has not been systematically/fully described. We aimed to compare the behavioural and developmental characteristics of children with SYNGAP1-ID to children with other monogenic causes of ID.

Methods: Participants were identified from the IMAGINE-ID study, a national study of neuropsychiatric risk in children with ID of known genetic origin. Thirteen individuals with SYNGAP1 variants (age 4-16 years; 85% female) were matched (2:1) with 26 controls with other monogenic causes of ID for chronological and mental age, sex, socio-economic deprivation, adaptive behaviour and physical health difficulties.

Caregivers completed the Development and Wellbeing Assessment (DAWBA) which provides DSM-5 diagnoses, as well as a physical health questionnaire.

Results: Children with SYNGAP1-ID were not more likely to meet criteria for autism ($N_{control}$=8 vs $N_{SYNGAP1}$=6; p=.35), attention-deficit hyperactivity disorder ($N_{control}$ =4 vs $N_{SYNGAP1}$=2; p=1), generalised anxiety disorder ($N_{control}$ =4 vs $N_{SYNGAP1}$=1; p=.49) or oppositional defiant disorder ($N_{control}$=0 vs $N_{SYNGAP1}$=1; p=.15) than controls.

Children with SYNGAP1-ID were more likely to be non-verbal (n= 8) than controls (n=6; p=<.01). SYNGAP1-ID children that were able to speak (n=5, M=3.25 years) achieved this milestone at the same age as controls (M=3.25 years; p=.84). However, caregiver-estimated language age was lower in SYNGAP1-ID (M=2.7 years) compared to controls (M=4.8 years; p=0.040). No difference in age of walking was observed between SYNGAP1-ID (M=2.3 years) and controls (M=2.2 years; p=.30). Seizures affected children with SYNGAP1-ID (n=11[84.6%]) more frequently than controls (n=2[7.6%], p=<0.001).

Conclusions: Children with SYNGAP1-ID have language difficulties beyond those observed in children with other monogenic variants when matched for developmental level. Early speech and language interventions should be provided to help address these difficulties.

Keywords: SYNGAP1, Intellectual Disability, Autism Spectrum Disorder, Language

13. Phenotypic Overlap Between Autism, Williams Syndrome and Angelman Syndrome

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Autism spectrum disorder (ASD), Williams syndrome (WS), and Angelman syndrome (AS) are among the most frequently contrasted conditions in cross-syndrome neurodevelopmental research. This originates from the observation that social development appears to be affected along opposite trajectories in these conditions, resulting in hyposociability in ASD and hypersociability in WS and AS. In this presentation we present recent research that challenges this long-held notion. In particular, there appear to be areas of overlap in social-cognitive processes and outcomes across conditions, alongside syndrome-specific patterns of social modulation of attention and imitative learning. We will illustrate the implications of this research with regards to the importance of parsing the construct of sociability to understand typical and atypical social development, and adopting transdiagnostic intervention approaches to target shared areas of needs across diagnostic boundaries.

Keywords: Autism, Williams syndrome, Social Learning, Imitation, Neurodevelopmental Conditions, Social Development

14. Critical Items of CBCLs in a Brazilian Sample of Williams and Down Syndrome Individuals

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Background: Williams (SW) and Down (DS) syndromes are associated with cognitive impairment and emotional and behavioural problems, that vary in topographies and severity. The Child Behavior Checklist for Ages 6-18 (CBCL/6-18) has critical items from the empirically based syndrome scales and DSM-oriented scales, which refer to severe emotional and behavioural difficulties. These items may raise challenges for management. This study investigated severe behavioural and emotional problems in Brazilian children and adolescents with WS and DS using CBCL critical items.

Methods: 96 parents of children with WS and DS participated (41 with DS, 60% boys, mean age=12.3 y/o (minimum 6, maximum 17), SD=2.59 and 55 with WS, 52% boys, mean age of 11.2 y/o (minimum 6, maximum 18), SD=4.19; age did not differ significantly between groups). CBCL critical items are scored as 0 (Not true), 1 (somewhat or sometimes true) or 2 (very true or often true).

Results: All parents from both syndromes endorsed 1 or 2 in at least one critical item. The items "Sees things that aren't there" (p=0.002; Z=-3.13; Effect size=-0.319), "Physically attacks people" (p=0.002; Z=-3, 15; Effect size=-0.321), "Deliberately harms self or attempts suicide" (p=0.049; Z=-1.97; Effect size=-0.201), and "Wets Self during the day" (p=0.004; Z = -2.89; Effect size=-0.294) had higher scores for the WS group. The only item in which the group with DS showed worse indicators was "Sets fire" (p=0.023, Z=-2.27; effect size: 0.231).

Conclusion: Both syndromes had indicators of severe emotional and behavioural problems that require special mental health attention. Individuals with WS in the sample had higher scores, indicating a more worrying profile. In addition to the fundamental need for individualized assessments and interventions, Brazilian individuals must receive more mental health services, especially in the elaboration of public policies since there are no official guidelines for rare syndromes like WS in Brazil.

Keywords: CBCL/6-18, critical items, Down syndrome, Williams syndrome, emotional and behavioural problems

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15. The eXtraordinarY Babies Study: Utilization of Early Intervention Therapies in 289 Children with a Prenatal Diagnosis of Sex Chromosome Aneuploidy (XXY, XYY, Trisomy X) and Relationship of Speech Therapy to Speech-Language Outcomes at 36 months of age

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Background: Sex chromosome trisomy (SCT) occurs in 1:500 newborns and is associated with increased risk of developmental delays. The eXtraordinarY Babies Study is a natural history study of prenatally-identified children with SCT aiming to characterize health and neurodevelopment from infancy and identify predictors of outcomes. This project aimed to: (1) Describe the utilization of early intervention (EI) therapies in young children with XXY, XYY, and Trisomy X, and (2) compare language outcomes at 36-months of age between 3 groups: no previous speech therapy (ST), proactive ST due to increased risk, and ST initiated in response to identified speech delay.
Methods: Infants with prenatally identified SCT (n=289; 189 XXY, 34 XYY, 66 XXX) enrolled in the study prior to 12 months. Demographic information, medical, developmental, and EI history were collected at 12, 24, and 36 month visits. Reason for initiation of speech therapy was coded as proactive or reactive. Expressive and Receptive communication scaled scores (SS) from the Bayley-3 were analysed by ANOVA in relationship to independent variables of ST subgroups. The Bayley-3 subset was limited due to COVID-19 visit restrictions.
Results: 58% of participants received at least 1 type of EI therapy, mean age of initiation 9.9 months (SD 6.22, 0-34m). There were no differences between SCT subgroups, thus all 3 diagnoses were pooled for analyses. ST and PT were most common therapy types (40%), followed by OT and Developmental therapy. There were no differences in race, ethnicity or SES of those who did and did not receive EI therapy. Of those who completed a 36-month assessment using the Bayley-3 (n=65), 35% received proactive ST, 25% received reactive ST, and 40% did not receive EI ST. Receptive language SS did not different between groups (p=0.21), while expressive language SS was lower in the reactive ST group compared to the proactive and no ST groups (7.2±3.5 vs 10.6±2.2, 9.4±2.6; p=0.046)
Conclusion: Understanding the utilization of early intervention therapies in young children with SCT can help guide genetic counselling and medical care recommendations for the growing population of infants with prenatal SCT diagnoses. Future analyses of therapy duration and individual change over time will further clarify changes in outcomes related to speech therapy.

Keywords: XXY, Klinefelter, XYY, Trisomy X, early intervention, speech therapy

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16. Anxiety in Turner Syndrome: Engaging Community to Address Barriers and Facilitators to Diagnosis and Care

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Background: Turner syndrome (TS) is a genetic condition caused by complete or partial loss of the second sex chromosome, affecting 1/2000 females. The TS community identifies anxiety as a major contributor to reduced quality of life. This study aimed to improve understanding of anxiety symptomatology in individuals with TS and to identify barriers and facilitators to diagnosis and care.
Methods: A mixed methods study design integrated community engagement through an online survey (N=135) followed by in-depth interviews (Caregivers=5, Individuals with TS=5). Descriptive statistics summarized survey results. Team-based rapid analysis synthesized interview findings to develop overarching themes.
Results: Participants with TS represented diverse ages (Caregiver survey: 12y±6; individual with TS survey: 26y±12) and geographical locations. Most identified as white (93.4%) and non-Hispanic (90.0%), and caregiver respondents had high educational attainment and annual income. Half of respondents reported experiencing anxiety symptoms 4 or more days per week, and caregivers and individuals reported anxiety affects their daily life (mean of 4.2 and 5.1 out of 10 respectively). Individuals with TS reported *feeling* anxious more often at school/work, while both caregivers and individuals reported anxiety expression increased at home. Insomnia was the most common symptom of anxiety endorsed across age and rater groups. Children were primarily triggered by stimulating environments and medical appointments and displayed aggression and hyperactivity as symptoms of anxiety. Perceived anxiety symptoms in adolescents included clinging and rumination and were triggered by conflict and increased expectations. Therapy and medication were rated as helpful when used, and use increased with age. Qualitative themes were: Anxiety impacts the whole family, TS creates a unique anxiety experience, and there are opportunities for early identification and intervention.
Conclusions: Anxiety in TS presents differently across the lifespan and may necessitate a nuanced, TS-informed and family-systems approach to diagnosis and care.

Keywords: Turner syndrome, anxiety disorders, community-based participatory research

17. KEYNOTE: Did We Take the Right Train in Promoting the Concept of 'Neurodevelopmental Disorders'?

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Background: The notion of neurodevelopmental disorder emerged at the beginning of the 21st century and quickly became a widely used concept in child and adolescent psychiatry. It reassures us about the etiology of mental disorders and has a certain theoretical consistency. However, it raises many questions: clinical, sociological, and epistemological.
Methods: Historical review of the concept of neurodevelopmental disorder followed by an epistemological perspective.
Results: From a clinical point of view, the most severe forms of ASD, ADHD, intellectual disabilities, or specific learning disorders are indeed compatible with the definition of an NDD. However, this is no more true for the mildest forms of these phenotypes. Psychiatrists and society accept now that autism corresponds to a different way of existing, the intensity of which can vary in important proportions so that the same word "autism" can be used to label very different children. For some of them, invoking a problem of "biological maturation of the CNS" raises ethical concerns.
Conclusions: In psychiatry, there is a very sad history of pathologizing psychological differences. We should pay more attention to how our societies receive the concepts we develop.

Keywords: Identity, neurodevelopmental disorders, autism, psychiatric diagnosis, brain mind problem

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18. An Open-Label Trial Assessing Short- and Long-Term Tolerability and Efficacy of ZYN002 (Cannabidiol) Administered as a Transdermal Gel to Children and Adolescents with 22q11.2 Deletion Syndrome (INSPIRE)

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Background: Behavioural problems and anxiety occur frequently in 22q11.2 deletion syndrome (22q). ZYN002 is a pharmaceutically produced cannabidiol transdermal gel. INSPIRE was an open-label, phase 2 trial evaluating safety/tolerability and efficacy of ZYN002 in individuals ages 4 to <18 years, in treating behavioural and anxiety-related symptoms in 22q.

Methods: Individuals having a Clinical Global Impression-Severity (CGI-S) score ≥4 and a Pediatric Anxiety Rating Score-Revised (PARS-R) score ≥10 were enrolled. Patients received 250 or 500 mg/day (weight-based) added to current therapy for 14 weeks (Period 1). Patients with ≥35% improvement in Aberrant Behavior Checklist-Community (ABC-C) Irritability at week 14 could continue for an additional 24 weeks (Period 2). Safety assessments included adverse events (AEs), vital signs, laboratories, and electrocardiograms (ECGs). Efficacy assessments included the PARS-R, Anxiety, Depression and Mood Scale (ADAMS), ABC-C and CGI-Improvement (CGI-I).

Results: Twenty patients, 60% males, mean age of 9.9 years enrolled. Seventeen patients completed Period 1 and 13 patients entered Period 2. Statistically significant improvements occurred in the PARS-R, ADAMS and ABC-C at Week 14. Percent improvement from baseline were PARS-R: Total Score 40.6%, p=0.0005; ADAMS: Total Score 45.3%, p=0.0005; General Anxiety 43.6%, p=0.0005; Depressed Mood 50.3%, p=0.0033; Social Avoidance 41.3%, p=0.0084; Obsessive/Compulsive Behaviour 64%, p=0.0037; Manic/Hyperactive Behaviour 38.2%, p=0.0032; and ABC-C: Social Withdrawal 27.6%, p=0.011; Inappropriate Speech 18.3%, p=0.0166; Stereotypic Behaviour 52.1%, p=0.0155; Irritability 36.3%, p=0.0055; Hyperactivity 16.5%, p=0.0091. Ten of 16 patients (62.5%) were "much improved" or "very much improved". Improvements at Week 14 were sustained through Period 2. Over 38 weeks, 3 patients reported treatment related AEs, all mild application site events. One patient discontinued due to AEs not related to ZYN002. Four non-treatment-related serious AEs were reported. No clinically significant changes in vital signs, ECGs or laboratories were reported.

Conclusions: ZYN002 was well tolerated and improved behavioural and anxiety-related symptoms in 22q. Further studies are warranted.

Keywords: 22q11.2; anxiety, behavioural problems, cannabidiol

19. PROM4RARE: Giving a Voice to Individuals with Rare Genetic Neurodevelopmental Disorders

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Background: In order to improve quality of care for individuals with rare genetic neurodevelopmental disorders (RGND), it is essential to measure patient reported outcomes (PROs). PROs represent the patient perspective on their health status and functioning. PROs can be measured with patient reported outcome measures (PROMs), which are standardized questionnaires completed by the patient. The aim of this study was to identify relevant PROs for individuals with RGND. This study serves as the initial phase towards the development of a PROM set for RGND.

Methods: A qualitative study was performed using in person or online focus groups and semi-structured interviews with adolescents and adults with RGND, caregivers, healthcare professionals, and patient representatives from the European reference network ITHACA. A focus group- and interview guide was developed including two themes: the impact of RGND on daily life and important PROs to discuss with the healthcare professional during the consultation. Data collection took place until data saturation was reached. All sessions were recorded and transcribed verbatim. Transcripts were analyzed by three researchers using a thematic analysis approach. PROs were clustered according to an integrated model for health outcomes, modified from Wilson and Cleary (1995) and the International Classification of Functioning (ICF).

Results: Ten focus groups (total n= 50 participants) and 13 interviews were conducted. Seven adolescents and 10 adults with RGND, 12 caregivers, 13 healthcare professionals, and eight European patient representatives participated. Data saturation was reached. Preliminary findings indicate that prominent themes reported by participants were related to sleep, anxiety, stress experiences, communication, behavior, and sensory integration problems.

Conclusion: Awareness for relevant PROs for individuals with RGND is important. By incorporating PROs in healthcare for RGND, personalized care will be fostered. The identified PROs will be used for the development of a PROM set for RGND.

Keywords: Rare genetic neurodevelopmental disorders, patient reported outcomes (PROs), patient reported outcome measures (PROMs)

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20. Associations Between Executive Functioning, Intolerance of Uncertainty and Behaviours that Challenge in SATB2-Associated Syndrome

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Background: Behaviours that challenge (BtC) are reported frequently in SATB2-associated syndrome (SAS), a genetic syndrome characterised by intellectual disability, severe speech delay, and palatal and dental problems. Estimated prevalence rates of 77% and 42% are reported for behaviours directed towards others (e.g., hitting, hair pulling) and the environment (e.g., throwing or tearing items), respectively. In mixed-methods research, caregivers often indicate these BtC are associated with uncertain and unpredictable situations or environments. This study aimed to examine whether these associations are underpinned by differences in executive functioning.

Methods: Caregivers of 37 children and adults with SAS (M_{age} 13.34 years; range 4-40 years; 51.3% male) completed questionnaire measures of adaptive functioning, frequency and severity of BtC, executive functioning (EF) and intolerance of uncertainty (IU). Correlation and bootstrapped mediation analyses were conducted.

Results: Significant associations were found between more severe and frequent BtC, increased IU, and lower EF (*ps* ≤.01). Higher levels of adaptive functioning were associated with increased EF ability (*p*=.003). Mediation analyses controlling for adaptive functioning indicated significant total and non-significant direct effects between IU and BtC frequency (*β*=0.13, *p*=.03; *β*=-0.03, *p*=.67) and IU and BtC severity (*β*=0.15, *p*<.001; *β*=0.09, *p*=.10). Significant indirect effects through EF were found between IU and BtC frequency and severity (*β*=0.15, 95% CI [0.07, 0.10]; *β*=0.15, 95% CI [0.02, 0.15]).

Conclusion: EF fully mediated associations between IU and the frequency and severity of BtC, suggesting lower EF ability reduces the ability to manage and respond to uncertain and unpredictable environments and situations. These findings indicate EF and IU should be considered when implementing person-centred support and interventions for BtC in this group. Fine-grained understanding of the profile of specific EF components, such as inhibition and cognitive flexibility, will increase understanding of EF as a mechanism underpinning BtC and further inform support and intervention strategies in SAS.

Keywords: SATB2-associated syndrome, SATB2, Behaviours that Challenge, Executive Function, Intolerance of Uncertainty

21. Autism Picture Tool: Children and Young People's Views on Consent

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Background: Many UK NHS autism assessment services have long waiting lists. Tools that help clinicians triage children at risk, to reduce those waiting times, are urgently needed. Our project developed an online autism screening tool, for use with children 4-11 years of age. The Autism Picture Questionnaire (APQ) was designed for online application by clinicians, for use with families from ethnic minorities, where English is not the first language, or low literacy. The task presents parents with photographs of children from diverse ethnic backgrounds, some have autism, others not, and illustrate key autism traits (e.g., lack of eye contact, stimming).
Methods: Obtaining informed consent to photograph children <16years was complex. We conducted co-production PPI focus groups with children from the Great Ormond Street Hospital Young Person Advisory Group (GOSH-YPAG).
Results: GOSH YPAG involvement proved valuable, informing both the design procedure and the acceptability of the APQ: (1) Benefits: The project was regarded as important, and the use of pictures facilitated accessibility and engagement. (2) Stigma: YPAG recommended the APQ contained a statement that it illustrates both autistic and non-autistic children. (3) Informed consent: the children illustrated were too young to consent. There were mixed views on whether they should be recontacted for consent when age 16. (4) Autism: YPAG recommended we devise a simple account of autism that could be given to affected children; we wrote the 'Autism Explainer Document' in collaboration with autistic children and their parents from the Autistica Charity Research Insight Group.
Conclusion: Co-production with children and young people facilitates the production of ethical research study materials and procedures. Our experience with children's focus groups led to the development of a unique psycho-educational leaflet and to an understanding of appropriate consent procedures for a novel autism assessment tool.

Keywords: Autism, co-production, young people, PPI, participation

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22. KEYNOTE: Development of Targeted Treatments for Rett Syndrome

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Rett syndrome (RTT) is a severe neurodevelopmental disorder (NDD), characterized by multiple impairments, which affects predominantly females. Until March 2023, no drug treatments were available for RTT's core symptoms. The recent approval of trofinetide by the FDA and the beginning of gene therapy trials represent major achievements with profound implications. They also represent a culmination of a process that began before the identification of mutations in the *MECP2* gene as the main cause of RTT.

Knowledge on the pathology and neurochemistry of RTT and development of mouse models of Mecp2 deficiency have been instrumental in both identifying and validating new treatments. Availability of disorder's natural history data has also been a major contributor. Efforts in the U.S.A., Europe, and Australia at characterizing the range and evolution of neurobehavioral and systemic manifestations of RTT have allowed the most adequate selection of trial participants and the development of outcome measures.

The success of trofinetide's studies, in combination with positive results of the mecasermin (recombinant human IGF-1) and blarcamesine (sigma-1 receptor agonist) drug development programs, support strategies targeting multiple cell signalling pathways and endogenous homeostasis for ameliorating the numerous and greatly impairing symptoms of RTT, even in adults. These improvements have been observed despite short duration treatments and suboptimal endpoints. Consequently, drug trials have facilitated the testing of therapies with even greater potential: attempts at correcting the genetic defect underlying RTT. Early information supports the safety of gene therapy in RTT; however, more time will be needed to determine their efficacy. The approval of a drug targeting core features of RTT has changed the stakeholders' mindset, becoming not the end of a pathway but rather the first step in developing new treatments (even combining approaches). This and other learned lessons should be carefully examined by others in the NDD field.

Keywords: Rett syndrome, neurodevelopmental disorders, drug trials, gene therapy, mouse models, natural history, outcome measures

23. Open Label Trial of Sulforaphane in FXTAS

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Background: The Fragile X premutation, 55 to 200 CGG repeats in *FMR1*, can cause neurodevelopmental disorders, neuropsychiatric disorders and in aging it can cause the Fragile X-associated Tremor Ataxia Syndrome (FXTAS), a neurodegenerative disorder. The premutation is associated with elevation of *FMR1* mRNA which causes RNA toxicity characterized by oxidative stress, mitochondrial dysfunction and early neuronal and astroglial cell death. Sulforaphane (SFN) is a sulfur containing compound, found in cruciform vegetables including broccoli, cauliflower and Brussel sprouts, that activates the Nrf-2 pathway which in turn stimulates the production of antioxidant enzymes and also enhances mitochondrial biogenesis.

Methods: 15 premutation carriers with FXTAS were given oral sulforaphane titrated up to 6 tablets per day of Avmacol (1275 mg/day) in the first 2 weeks and then treated for 6 months at their maximal tolerated dosage. Baseline measures included quantitative assessment of tremor (Kinesia One) and ataxia (GaitRite), neuropsychological measures (MoCA,CANTAB,BDS2), emotional measures (SCL-90R) and molecular biomarkers including FMRP levels. Eleven patients completed the 6 month trial and outcome measures. One patient dropped out early and 3 were unable to return for the follow-up assessment.

Results: No significant changes were seen in the tremor and ataxia measures but the Spatial Working Memory errors improved from 22.6 (SD 4.74) to 18.2 (SD 6.37) (p=0.048) and the MoCA improved from 25.5 to 27.25 (p=0.099). A surprising finding was improved levels of FMRP in 4 patients and these correlated with improvements on the neuropsychological measures.

Conclusion: Sulforaphane was well tolerated and safe but there were no significant benefits to the tremor and ataxia. FMRP levels increased in 4 patients who had stage 2 and 3 FXTAS and the increase in FMRP, which was almost twice baseline in two patients, correlated with improvements in neurocognitive measures. A controlled trial is warranted.

Keywords: Sulforaphane, FMRP, FXTAS, neurocognitive, premutation

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24. High Frequency of Neuropsychiatric Disorders and a Need for Treatment in Patients with FXAND Linked to FMR1 Gene Premutation Carriers

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Background: Fragile X messenger ribonucleoprotein 1 (*FMR1*) gene premutation (PM) is linked to a higher frequency of anxiety, attention-deficit hyperactivity (ADHD), depression, autism spectrum disorder (ASD) and other Diagnostic Statistical Manual-5 (DSM-5) diagnosis under umbrella of fragile X-associated neuropsychiatric disorders (FXAND), which often requires treatments.

Methods: We examined for frequencies of FXAND and types of the treatments in a clinically ascertained cohort of 17 patients (76.5% paediatrics 8/13, 61.5% males; median age 12.0 yo) with PM (55-199 CGGs) from Fragile X Clinic at Kennedy Krieger Institute, approved by the Johns Hopkins's Institutional Review Board.

Results: All patients had FXAND: anxiety and ADHD (70.6%), learning disabilities (52.9%) mostly in paediatrics, depression mostly in adults (29.4%), ASD (17.7%; all ≥ 100 CGGs), language disorders (17.6%). The study's cohort mean number of CGG repeats was 82.50 ± 20.71. *FMR1* gene protein (FMRP) level was 15.54 ± 10.84 pg/ng available for 29.4% of those patients. The vast majority (70.6%) of patients were on at least 1 psychotropic drug, SSRI were the most prescribed (47.1%). Non-drug treatments (41.2%) driven by paediatric patients had: 23.5% both speech-language and occupational, 17.6% behavioural, and 5.9% applied behavioural.

Conclusion: The clinical *FMR1* PM cohort of both sexes had an extremely high frequency of FXAND: all had at least 1, 65% had 1-2 and 35% had 3-4 FXAND driven by anxiety and ADHD in 70% of the paediatric cases, slightly more affected were males. Depression was found in adults. The vast majority of them (71%) received psychotropic drug treatment, and 41% of them also had non-drug treatments driven by the paediatric population. The study contributes pilot data as for need to early diagnose and treat patients with the *FMR1* gene PM-associated FXAND, to educate multispecialty clinicians, and to facilitate a such system-based interdisciplinary effort.

Keywords: FMR1 gene premutation, DSM-5 FXAND diagnosis, drug and non-drug treatments

25. Fragile X Syndrome and FMR1 Premutation: Results From a Survey on Associated Conditions and Treatment Priorities in Italy

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Background and objectives: Fragile X Syndrome (FXS) is the most common cause of inherited intellectual disability, caused by CGG-repeat expansions (<200) in the *FMR1* gene leading to lack of expression. When the CGG trinucleotide repeats between 55 and 200 times, there is a diagnosis of *FMR1* premutation. Individuals with PM are at risk for a range of clinical conditions, including primary ovarian insufficiency (FXPOI), fragile X-associated neuropsychiatric disorders (FXAND) and fragile X-associated tremor/ataxia syndrome (FXTAS). Although there is not a current cure for FXS and PM, timely diagnosis as well as the implementation of treatment strategies, psychoeducation and behavioural intervention may improve the quality of life (QoL) of people carrying FXS or PM. With the aim to investigate the main areas of concerns and the priorities of treatment in these populations, the Italian National Fragile X Association in collaboration with Bambino Gesù Children's Hospital, conducted a survey among Italian participants.

Method: Here, we present a survey based on a previous study aimed to investigate the main symptoms and challenges in American individuals with FXS. The survey has been translated in Italian in order to explore FXS needs of treatment also among Italian individuals affected by FXS, family members, caretakers and professionals. Additionally, we added a section designated only to people carrying the *FMR1* PM, to investigate the main symptoms, daily living challenges and treatment priorities.

Results: Italian survey was launched in November 2022 and will be closed in May 2023. Results will be presented at the conference and compared with previous studies in research.

Conclusion: FXS and PM can be associated with a range of cognitive, affective, and physical health complications. Taking a patient-first perspective will help clinicians to better characterize the cognitive-behavioural phenotype associated to these conditions, and eventually to implement tailored therapeutic approaches.

Keywords: FMR1 gene; developmental disorders; fragile X syndrome; FMR1 premutation; voice of the patient; treatment.

26. The Relationship between Autism Characteristics, Intolerance of Uncertainty, and Anxiety in Fragile X Syndrome

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Background: People with fragile X syndrome (FXS) often experience co-occurring anxiety and autism; however, characterising and distinguishing anxiety is challenging due to overlap with autistic characteristics. Autism characteristics, such as sensory sensitivities and restricted/repetitive behaviours (RRBs), are common in FXS and may be associated with an increased likelihood of anxiety. Furthermore, studies indicate that intolerance of uncertainty (IU) may serve as a risk factor for the development and maintenance of anxiety and may mediate the relationship between anxiety and autism characteristics for autistic individuals. Characterising the relationship between autism characteristics, IU, and anxiety is essential to informing anxiety interventions and theoretical models for people with FXS. This study investigates the relationship between sensory sensitivities, RRBs, IU, and anxiety in people with FXS (n = 26, Mage = 28.08 years).

Methods: Parent-reported sensory sensitivities, RRBs, and IU were assessed using the Sensory Experiences Questionnaire (SEQ), Repetitive Behaviour Questionnaire (RBQ), and Responses to Uncertainty and Low Environment Structure (RULES), respectively. Parent-reported anxiety was determined using the Anxiety, Depression and Mood Scale (ADAMS).

Results: Pearson correlations revealed that sensory sensitivities [p = 0.008], RRBs [p = 0.030], and IU [$p < 0.001$] were positively associated with anxiety in FXS.

Conclusion: These results suggest that people with FXS that experience greater difficulties with sensory sensitivities, RRBs, and tolerating uncertainty are more likely to experience anxiety. Although additional work is needed, understanding the underlying factors that contribute to the relationship between autism characteristics, IU, and anxiety in rare genetic syndromes will serve to improve theoretical models and targeted interventions.

Keywords: Fragile X syndrome, anxiety, autism, intolerance of uncertainty

Abstracts for Poster Presentation

(in alphabetical order)

POSTER 1: Fragile X-Associated Neuropsychiatric Disorders (FXAND) in Young Fragile X Premutation Carriers.

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Background: The Fragile X premutation carrier state (PMC) (defined by presence of 55 - 200 CGG repeats in the *FMR1* gene) has been found to be associated with several conditions including FXPOI and FXTAS in older PMC's. We aimed to identify the prevalence of common neuropsychiatric disorders (FXAND) in a sample of young PMC.
Methods: This was a retrospective study conducted by medical record review of PMC's who were seen either for clinical concerns or identified through family testing of an affected sibling with Fragile X syndrome. Information on the presence of ASD, ADHD, anxiety, depression and obsessive-compulsive disorder (OCD), long-term psychiatric medication intake, molecular (CGG repeat and *FMR1* mRNA), and cognitive results were included in the analysis.
Results: Participants included 63 individuals (55 males) aged 7.8 to 20.0 years (mean 12.5 ± 3.3). CGG repeat mean was 96 ± 41.2; 14 (22%) had >120 CGG repeats. Number of CGG repeats correlated positively with *FMR1* mRNA levels (r^2=0.87, p<0.001), and mean mRNA level was 2.8 ± 1.1. Mean FSIQ was 89.2 ± 23.2. ASD was present in 21 (33.3%) individuals (18/55 males and 3/8 females) with significantly lower FSIQ in those with ASD (mean 74.6 vs 97.3, p =0.003). ADHD was present in 68.3%; (42/55 males and 1/8 females, $X^2 = 21.6$, $p < 0.001$). The majority (N=53; 84.1%) had at least one mental health disorder with anxiety being the most common (79.4% of subjects), OCD (30.2%), phobia (27.0%), and depression (19.0%). Almost all (93.7%) were on ≥ 1 long-term medication (stimulants and sertraline being most common).
Conclusions: This study demonstrates a high prevalence of FXAND diagnoses, although this is a convenience sample that was biased because of clinical referrals for behavioral or cognitive problems. Clinicians should be aware of this and assess even young PMC for these problems, as early intervention is crucial for their comprehensive care.

Keywords: Fragile X premutation, FXAND, ADHD, autism

POSTER 2: The Importance of Distinguishing Within- and Between- Person Effects in Natural History Studies of Genetic Conditions Associated with Neurodevelopmental Disorders

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Background: Developmental processes (e.g., language, cognition, social skills) are often concepts of interest in clinical trials for rare genetic conditions affecting neurodevelopment (GCAND). Due to the rareness of GCAND, extant natural history data may be used as external control in these trials. This practice carries the potential for cohort effects, as differences between older and younger natural history study participants may be due to something other than development, such as changing diagnostic practices or psychometric properties of instruments. Thus, investigators must pay special attention to the operationalization of time and disentangling of cross-sectional (e.g., cohort) and true longitudinal (e.g., within-subject) effects of age.

Methods: Example data are shown from an anonymized GCAND natural history study where participants were followed for up to 3 years (N=89). The decomposition of age into between-subject (cross-sectional, or differences between older and younger participants) and within-subject (longitudinal, or change that occurs within a person) components is described. The resulting variables are used as predictors of IRT-based ability scores on a commonly used clinical outcome assessment (Vineland Adaptive Behavior Scale, Personal Skills subdomain) in a multilevel framework, and the results are compared to a naïve analysis with the original age variable as the lone predictor.

Results: The comparison of the decomposed model to the naïve model revealed evidence of a cohort effect, as the annualized rate of change within person was faster than would be expected given the between-person difference of older and younger participants. As a result, the naïve model estimated slower within-person change with too much precision.

Conclusion: In this study, naïve analysis underestimated the rate of development with inflated precision. Natural history studies of GCAND are an essential source of information on the expected trajectory of the disorder, and careful modelling can be used to avoid such errors.

Keywords: Longitudinal data, natural history study, cohort effect, statistics

POSTER 3: Co-occurrence of Anxiety & Autism in Fragile X Syndrome

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Background: People with fragile X syndrome (FXS) are more likely to experience co-occurring anxiety and autism compared to the general population. Recent studies suggest that people with FXS display syndrome-specific profile of anxiety and autistic characteristics; however, it is unclear how these two interact. A greater understanding of the behavioural manifestations of anxiety is needed to improve diagnosis and access to subsequent support. This study aims to investigate the prevalence and co-occurrence of anxiety and autistic characteristics in people with FXS. The profile of anxiety was compared for people with FXS with a higher likelihood of autism and people with FXS with a lower likelihood of autism.

Methods: This study included data from 49 people with FXS. The Generalised Anxiety subscale of the Anxiety, Depression and Mood Scale (ADAMS) was used as a measure of anxiety. The likelihood of co-occurring autism was determined using the Social Communication Questionnaire (SCQ). The anxiety and autism threshold scores were >10 ADAMS and >22 SCQ.

Results: 61% of people with FXS were likely to experience autism and 32% of people with FXS presented with symptoms associated with generalised anxiety. A two-sided Fisher's test revealed there was no significant co-occurrence between anxiety and autism in people with FXS ($p > 0.9999$). Nervousness and the inability to relax were noted as more severe for people with FXS with a higher likelihood of autism. Being worried or anxious was a greater concern for people with FXS with a lower likelihood of autism.

Conclusion: Further research is needed to understand the presentation of anxiety in people with FXS, and how that may differ for people with and without a co-occurring autism diagnosis. The results suggest that although present, anxiety does not commonly co-occur with autism in people with FXS. This may be partly due to the low sample size.

Keywords: Fragile X syndrome, anxiety, autism

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POSTER 4: Translation of International Registries to Improve Understanding of Diagnostic Patterns and Access to Diagnostic Services in Angelman Syndrome

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Background: Angelman syndrome (AS) is a rare neurogenetic condition affecting approximately 1 in 15,000 individuals, or 500,000 individuals worldwide. International registries are critical to capturing common patient related information on rare diseases, as they allow patients or their caregivers to provide information in a safe and accessible manner. The Global Angelman Syndrome Registry (GASR) was launched in English in 2016. The GASR adopted a novel approach using crowd-sourcing and machine translation tools leading to the availability of the GASR in Spanish, Traditional Chinese, Italian, and Hindi. The languages have been accessible to users since 2022. As a result, enrolments increased by 124% percent for Spain, 67% percent for Latin America, 46% percent for Asia, 24% for Italy, and 43% for India.
Methods: The authors examined the proportion of deletion and non-deletion sign ups per region of 906 individuals with AS who were signed up to the GASR by their families between 2016 and 2022.
Results: On average, 65% of patients were diagnosed with a deletion, compared to 35% for non-deletion aetiology including a mutation, unipaternal disomy (UPD), imprinting centre defect (ICD) or mosaic. Rates of deletion diagnosis were significantly lower than average in Asia (50%) and Northern America (60%), although participation numbers were low in Asia at 38 individuals. Diagnosis rates of deletions were slightly higher in Latin America and the Carribbean (72%) and Oceania (71%), and average in Europe (67%).
Conclusion: Findings indicate that the ratios of deletion and non-deletion diagnoses in AS vary by region, suggesting possible differences in awareness of the syndrome, or access to clinical expertise and diagnostic tests. Further research as more families join the registry would create a better understanding of diagnostic patterns and resources worldwide.

Keywords: Angelman syndrome, disease registries, language translation

POSTER 5: Engagement in a Behavioural Intervention for Toddlers with Tuberous Sclerosis Complex

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Background: Tuberous sclerosis complex (TSC) is a genetic disorder characterized by neurodevelopmental conditions, including epilepsy and autism. Toddlers diagnosed with TSC and their families often contend with numerous medical intricacies and therapeutic demands, which may disrupt the consistency of engagement in behavioural interventions. This research seeks to understand the variability in engagement in a remote, parent-mediated behavioural intervention and identify the determinants leading to discontinuation of the program.
Methods: Families (n = 58) were consented for a remote-delivered naturalistic, developmental, behavioural intervention (JASPER) with certified coaches. Sessions were offered weekly for approximately one hour over 12 weeks. Through a multi-methods approach, data was sourced from both parent and interventionist surveys spanning quantitative and qualitative paradigms, along with clinical assessment data. Using logistic regression, behavioural, clinical, developmental, and family demographic characteristics were analysed against program discontinuation.
Results: 25% of participants did not complete the intervention program, while 75% attended eight or more sessions (out of twelve maximum). Individuals who initiated treatment during the COVID pandemic were less likely to complete intervention (p=0.02). Near significant trends were similarly observed for families receiving more community based intervention (p=0.08). Younger participants and those in the waitlist treatment group trended towards being less likely to complete intervention (p=0.18 and p=0.19) Factors like autism diagnosis, developmental level, parent employment status, family income, and seizure activity did not significantly predict discontinuation.
Conclusions: External dynamics like the COVID pandemic and other community-based interventions were associated with discontinuation of the program, surpassing any clinical or familial determinants. These results suggest that parent-mediated interventions may be useful for families experiencing frequent medical disruptions, along with families accessing fewer community-based intervention; however, future work needs to explore additional barriers that may limit families obtaining effective services, including more personalized delivery of interventions.

Keywords: Genetic syndrome, epilepsy, autism, tuberous sclerosis complex, engagement

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POSTER 6: An Exploration of the Neurodevelopmental Phenotype of Two Patients with 48,XXYY During Infancy

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Background: 48,XXYY is a variant of 47,XXY occurring in approximately 1 in 18,00-50,000 male births. Though phenotypic features of adolescents and adults with 48,XXYY are widely reported on, reports in infancy are scarce. This case study aims to compare the neurodevelopmental profile of two patients with 48,XXYY during infancy and the possible effects of early hormonal therapy (EHT) on their neurodevelopmental outcomes.

Case I: Case I was prenatally detected as at-risk for 47,XXY via NIPTS screening, and 48,XXYY was confirmed after birth via CMA. He received EHT at 4, 5, and 6 months.

He presented with non-dysmorphic features and decreased muscle tone in the orofacial musculature secondary to associated truncal hypotonia. Neurodevelopmental abilities during the first year of life were within normal limits with no evident of delays. A right-side torticollis was observed.

Case II: Case II was prenatally diagnosed with 48,XXYY via amniocentesis and confirmed after birth by karyotype. Fetal MRI was completed, and a Dandy-Walker cyst was noted.

He was hospitalized for 6 weeks following delivery. He was born with a cleft of the soft palate and a torticollis to the left side. He exhibited poor feeding habits, a mild cardiac murmur, and transient tachypnea. The patient required supplemental oxygen and received nourishment via a nasal gastric tube for weeks. He had a febrile seizure at 12 months. He did not receive EHT.

Conclusion: The variability in the two infant presentations varies widely. Both cases contribute novel information on the phenotype of boys with 48,XXYY in infancy. In the first case, advanced neurodevelopmental abilities may potentially be attributed to the EHT and reduced medical complications during infancy. These cases highlight the benefits of prenatal detection, and a comprehensive multidisciplinary evaluation to determine the appropriate therapeutic services. The variability of these two prenatally detected cases reveals the importance of early comprehensive care and consideration of EHT to facilitate mini-puberty and potentially neurodevelopment.

Keywords: Klinefelter Syndrome, Hormonal Replacement Therapy, Neurodevelopmental

POSTER 7: Evaluation of the MAP-DB among Individuals with SCN2A

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Background: *SCN2A*-related disorders (SCN2A-RD) are due to pathogenic variants in the *SCN2A* gene. *SCN2A*-RD is characterized by severe developmental and epileptic encephalopathy. Challenging and disruptive behaviours are also common and therefore could be important treatment trial outcomes. We evaluated the psychometric properties of the Multidimensional Assessment of Preschool Disruptive Behaviors (MAP-DB) in individuals with *SCN2A*-RD to evaluate its fitness for purpose in *SCN2A*-RD.

Methods: Families of 58 individuals (median 5.95 years, IQR=5.9; n=24, 41% female) with *SCN2A*-RD were recruited through the FamilieSCN2A Foundation. The MAP-DB quantified disruptive behaviours. The comprehensive Vineland-3 interview was also collected via examiner interview within 30 days of completing the MAP-DB. The Vineland Maladaptive Behavior raw scores provided evidence for convergent validity, and the adaptive behaviour subdomain growth scale values indexed discriminant validity. Test-retest reliability was evaluated on a subset (n=24) who repeated the MAP-DB within 10 weeks.

Results: Test-retest reliability was high (ICCs > 0.85). Convergent correlations with Vineland-3 Externalizing behaviours were high for Aggression (r=0.75) and Tantrums (r=0.66). Tantrums also had a moderate correlation with Internalizing behaviours (r=0.53). MAP-DB Mood scores were more strongly related to adaptive (median r=0.51, range 0.18-0.64) than maladaptive (Internalizing r=0.24, Externalizing r=0.27) behaviours. Discriminant validity was largely supported, except that MAP-DB scores was significantly positively related to motor functioning.

Conclusion: The MAP-DB exhibited adequate psychometrics among individuals with SCN2A-RD. The Mood scores exhibited somewhat poorer discriminant validity, suggesting that mood-related problematic behaviours may be harder for parents and caregivers to appreciate in the absence of other adequate adaptive behaviours. Interestingly, the Vineland motor subdomains were significantly related to the MAP-DB, suggesting that some problem behaviours require a baseline level of motor functioning in order for an individual to exhibit them. Given that motor functioning is highly variable in this population, modifications to the MAP-DB may need to be considered.

Keywords: SCN2A, MAP-DB, Vineland Adaptive Behavior Scales, Disruptive Behaviour, Reliability

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POSTER 8: Listening to People Living with PWS Across the World

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Background: Through speaking about inclusion and choice, people with disabilities have been able to better inform the policies surrounding employment and education. Self-advocacy has been linked to increased success in school, positive identity building, and improvement in problem behaviours. The International Prader Willi Syndrome Association (IPWSO) currently, involves parents and caregivers to advocate for people with PWS but is seeking to more directly involve people living with PWS to allow meaningful inclusion. There is limited previous research documenting the personal perspectives of people living with PWS, and this has focused on self-concepts, individuals' understanding of the syndrome and opinions regarding treatment. Our goal in this research was to better understand the perspectives of people living with PWS with regard to activities that will ultimately allow IPWSO to meaningfully involve people living with PWS in international PWS education and advocacy. To do this, we aimed to examine on an international scale, what people living with PWS believe is important for their lives, and how can they believe they can be supported to access these things.
Methods: The 'Listening to people living with PWS across the world' survey was developed in collaboration with professionals and caregivers with experience working with people living with PWS. The online survey explored opinions about people living with PWS coming together, the experiences of living with PWS, and self-advocacy. We received 123 valid responses from participants living with PWS across 15 countries. We examined the survey responses to inform the questions asked in follow up one-to-one interviews with volunteers living with PWS. The interviews are taking place remotely through video calls on zoom. We currently interviewed 4 English speaking participants and 2 Thai. We expect to have a minimum of 8 participants.
Results: We conducted a content analysis of the survey responses. The analysis determined the existence and frequency of 23 themes and 18 subthemes. The most frequent themes were socialising with family and friends, food consumption and management, and employment and education. Once the interviews are complete, we will carry out a reflexive thematic analysis to provide more depth information on individuals' views of the identified themes.
Conclusion: The results will shed light on what people living with PWS find important to talk about and what support they think they need to achieve the things that are important for them. The ultimate goal is to facilitate research into the importance of giving voice to people living with PWS and to gather information that will support PWS associations across the world in meaningful inclusion.

Keywords: Prader-Willi Syndrome, International Prader-Willi Syndrome Organisation, Advocacy, Inclusion, Support, Employment and Education

POSTER 9: Evaluation of Circadian Rhythm in SYNGAP1-Related Intellectual Disability

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Background: SYNGAP-related Intellectual Disability (SYNGAP1) is a rare single gene condition caused by variants in the SYNGAP1 gene. In addition to Intellectual Disability, autism, epilepsy and sensory sensitivities, sleep problems are consistently reported. Rodent data shows that the Syngap1 protein is a widespread negative regulator of biochemical pathways in the brain including in the suprachiasmatic nucleus an area central to the setting of circadian rhythm. Its expression is regulated over the circadian cycle and downstream behavioural consequences have been identified. Therefore, examination of circadian rhythm in people with SYNGAP1 is important, but to date no systematic case-control studies have been done.

We aimed to use actigraphy to study circadian rhythm patterns over the course of a week in children with and without SYNGAP1. We hypothesised that circadian rhythm disruption would be more prevalent in SYNGAP1. Methods: We collected 1 week of actigraphy data using the SOMNOwatch Plus (S-Med) in children with SYNGAP1 and a control group. Total Sleep Time (TST), Sleep Period Time (SPT – from first falling asleep to final wakening) and Wake After Sleep Onset (WASO - time awake after initially falling asleep) were measured. Sleep Efficiency (SE) was calculated as TST/SPT. Data was analysed using IBM SPSS Version 25.

Results: 15 children with SYNGAP1 and 15 controls were recruited. One from each group withdrew and one child with SYNGAP1 didn't tolerate the actigraph. WASO was significantly higher in the SYNGAP1 group compared with controls ($p = 0.002$) and SE was significantly lower ($p = 0.001$). No other statistically significant differences were found.

Conclusions: Almost all children with SYNGAP1 tolerated actigraphy watches despite their sensory sensitivities. Participants with SYNGAP1 were found to spend statistically more time awake after initially falling asleep and had decreased sleep efficiency compared to controls.

Keywords: SYNGAP1, Intellectual Disability, Sleep, Actigraphy

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POSTER 10: A Comprehensive Investigation in the Anthropometric Measurements of Males with 47,XXY (Klinefelter Syndrome) from 6-18 years

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Introduction: 47,XXY, or Klinefelter syndrome, is the most common sex chromosome aneuploidy (SCA). 47,XXY males characteristically present with hypotonia, decreased phallus size, and increased stature due to androgen insufficiency. Hormonal replacement therapy (HRT) has been shown to ameliorate these physical characteristics of 47,XXY. This retrospective, cross-sectional study investigated HRT and the impact on the growth of males with 47,XXY between the ages of 6 and 18 years old.

Methods: Our cohort is represented of 169 prenatally diagnosed males with 47,XXY between the ages of 6 and 18 years old. Growth was measured using height, weight, and head circumference. We analyzed these growth variables in one HRT group (T group) and a no treatment (No-T) control using a t-test.

Results: In prenatally diagnosed males between the ages of 6 and 18 years old, significant differences in head circumference were observed between the T group at ages 16.1 to 17.0 ($M = 57.1$, $p = 0.04$) compared to the No-T group ($M = 59.7$). Regarding height, significant results were observed at the age ranges of 12.1-13.0 for the T group ($M = 165.9$, $p < 0.05$) and No-T group ($M = 152.4$) and 16.1-17.0 years old for the T group ($M = 180.3$, $p = 0.004$) and for the No-T group ($M = 172.7$). Only the 12.1-13.0-year-old age group showed significant differences in weight between the T group ($M = 51.8$, $p = 0.02$) and no-T group ($M = 37.9$).

Conclusions: Our findings reveal that HRT does not significantly impact head circumference, height, or weight in a majority of the age ranges among prenatally diagnosed males with 47,XXY. In selected age ranges, boys who had testosterone weighed significantly more than those in the No-T group. Our findings demonstrate that HRT may facilitate the development of more muscle mass.

Keywords: Hormonal Replacement Therapy, Growth, Klinefelters Syndrome, Testosterone

POSTER 11: Molecular Biomarkers as Susceptibility/Risk of Development, Progression and Severity of FXTAS

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Background: The significance in identifying molecular biomarkers and changes in the associated pathways, can objectively point out changes in disease pathology, and therefore be crucial for improving patient outcomes. Importantly the identification of suitable biomarkers it will be significant for the early diagnosis treatment efficacy of this disease. Currently there are no treatment available to stop or slow down FXTAS progression, making the search for candidate protein markers more urgent. To better characterize the abnormal molecular phenotype, we quantitatively compared PBMCs of males premutation carriers (PM) who developed FXTAS overtime (CON) and compared to those without FXTAS (NCON) and to controls (HC), to identify potential proteins differentially expressed between the groups.

Methods: Proteomics analysis using mass spectrometry was carried out in 17 male PM carriers with (n=17, converters, CON at V2), and without (n=19, non-converters, NCON at V2) the diagnosis of FXTAS, and in 12 HC with similar age and gender distributions at two-times point, V1 and V2.

Results: Our preliminary data on the proteomic profile clearly show a different protein signature among the groups (CON vs NCON at both V1 and V2) and enrichment pathway analysis demonstrated the involvement of key pathways, including lipids, mitochondrial, neurodegeneration, in agreement with our previous metabolomic studies. Specifically, we identified 79 proteins which expression was altered in FXTAS patients, suggesting changes in cellular signaling, functioning, organization, growth and proliferation, in immune and inflammatory responses, in genetic information processing and mitochondrial function. Interestingly, 7 proteins that were found significantly differentially expressed in this study between PM with and without FXTAS overlap with those identified in a recent study carried out in CSF derived from FXTAS patients and healthy controls.

Conclusion: These findings provide insights for potential therapeutic targets that could lead to retardation or reversal of symptoms of FXTAS. Importantly the agreement between results obtained in the CSF and on PBMCs is of relevance as indicates that blood proteomic profile can inform us on potential underlying disease pathophysiology encouraging to shine light on the molecular mechanisms causing neurodegenerative diseases.

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POSTER 12: Longitudinal Phenotyping Results from the First Natural History Study of Creatine Transporter Deficiency

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Background: Creatine transporter deficiency (CTD) is a rare X-linked creatine deficiency disorder caused by mutations in the SLC6A8 gene; males with CTD typically exhibit limited language development and intellectual disability. The goal of this 4-year longitudinal natural history study of CTD (Vigilan; NCT02931682) was to enhance understanding of the medical and developmental phenotype of CTD, as well as to provide a basis for external control of later clinical trials.

Methods: Fifty males between the ages of 6 months and 65 years (baseline age, median=7.6 years, IQR=4.6 – 11.3; 75% white) with a documented pathologic mutation in SLC6A8 were enrolled and assessed with a neurodevelopmental battery (e.g., Vineland Adaptive Behavior Scales, 3rd Edition, Mullen Scales of Early Learning) at 6-month intervals. Annualized change as a function of the individuals' age was estimated using multilevel modelling.

Results: A total of 50 participants were enrolled. Nearly all developmental/cognitive scores were in the range of intellectual disability (<70), with an increasing proportion of participants falling into the severe (<35) category with age. On average, participants gained 2.5 [1.9, 3.1] months of Mullen Full Scale Mental Age (MA) per year, though this annualized change was slower for older individuals (0.27 months per year slower per year older than age 8 years). Vineland growth scale values (GSVs) similarly indicated increasing abilities within person that was slower for older participants than younger participants (e.g., annualized Expressive Language GSV = 4.7[3.5, 6.0], decreased by 0.57 units per year older than 8).

Conclusions: The results of the first longitudinal natural history study of CTD confirm that the developmental phenotype is marked by severe intellectual disability, and newly show that increasing levels of impairment are not due to loss of skills but rather stability or slower-than-expected growth.

Keywords: Creatine transport deficiency, growth scale values, longitudinal study, severe intellectual disability

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POSTER 13: A Clinical Behaviour Checklist for Children with Intellectual Disability and Complex Needs.

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Background: The Checklist Project aims to develop a clinical checklist for parents/carers and clinicians to use collaboratively, to help identify and monitor the potential causes of behaviours of concern (BoC) in children with a moderate-profound intellectual disability (ID). Children with moderate-profound ID and complex needs are at high risk for behaviours such as self-injury, aggression, and destructive behaviour. A number of common causes of these behaviours are often overlooked which can impact assessment and treatment.

Method: For phase 1, a checklist was co-produced with a team of parents/carers, clinicians and academics who work with children with ID and complex needs. Discussion included the checklist items, aims, design, information manual and practitioner guidance. For phase 2, a further consultation took place with two separate groups of parents/carers and clinicians to inform the final checklist. During phase 3, 70 parents and 10 paediatricians are being recruited within a mixed methods design to establish the feasibility and acceptability of implementing the checklist within paediatric services in local Special Schools. Convergent validity and test-retest reliability will also be assessed.

Results/Aims: It is expected that the checklist will support conversations about BoC between parents/carers and clinicians and that working through possible causes will help to enhance treatment pathways, reduce BoC, and reduce parental and child distress.

Conclusion: Phase 3 began in April 2023. The final checklist items are pain and discomfort, sensory avoidance or sensory seeking, anxiety, low mood, sleep difficulties, impulsivity, insists on sameness, strong social seeking, strong social avoidance, communication, and learned behaviour. The feasibility and acceptably findings will be ready to report in 2024.

Keywords: Moderate-to-profound, intellectual disability, checklist, behaviours of concern, children

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POSTER 14: Assessing Cognitive Flexibility With an Adapted Reverse Categorisation Task in Young Children With Down Syndrome

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Background: Individuals with Down syndrome (DS) are predisposed to challenges with aspects of cognitive regulation, including cognitive flexibility. 'Cognitive flexibility' involves the ability to adjust thinking in response to changes in information. Many children with DS may benefit from early intervention that strengthens cognitive flexibility foundations, however, accurate measurement of cognitive flexibility skills is necessary to advance treatment science in this area. Available measures of early childhood cognitive flexibility frequently require language and/or complex motor skills, which confound performance interpretations. The present study aimed to evaluate an adapted measure of early childhood cognitive flexibility that minimizes potential confounding skills.
Methods: Seventy-two children with DS 2.5-8 years completed an adapted reverse categorisation (ARC) task. A small subgroup (n = 28) also participated in this task two weeks later. ARC is a sorting task wherein participants sort by a color congruent rule before sorting by a color incongruent rule. Sorting demands were reduced by simplifying receptive language demands during instructions, using high-contrast sorting objects with familiar cultural referents, and providing teaching trials with demonstrations to participants.
Results: Post-switch performances were analyzed by child chronological and mental ages (CA and MA). Performance on post-switch trials increased with CA ($r_{70} = 0.58$, $p < .001$). A similar trend with increasing performance was observed for MA, with potential ceiling effects at 3 years ($r_{70} = 0.56$; $p < .001$). Performance varied most for children with an MA of 2 years. The task demonstrated preliminary test-retest reliability for post-switch accuracy (*ICC* (A,1) = .81; $F_{26,26} = 9.42$, $p < .001$).
Conclusion: Psychometrically validated outcome measures are necessary for measuring performances in research and treatment trials for children with DS. The ARC task demonstrated adequate developmental sensitivity and evidence of test-retest reliability. Future studies should examine its convergent and divergent validity with measures of other EF components.

Keywords: Down syndrome, measurement, executive function, cognitive flexibility

POSTER 15: PROM4RARE: Measuring What Matters For Individuals With Rare Genetic Neurodevelopmental Disorders

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Background: In order to improve quality of care for individuals with rare genetic neurodevelopmental disorders (RGND), it is essential to measure patient reported outcomes (PROs). PROs represent patient perspective on their health status and can be measured with patient reported outcome measures (PROMs). PROMs can be used in research to measure treatment effect and in clinical care to monitor and discuss symptoms and functioning. Unfortunately, the use of PROMs for individuals with RGND is scarce due to unsuitable and time-consuming questionnaires. The objectives of this project are (1) to develop a core PRO (CoPRO) set for RGND, (2) to select suitable generic PROMs with the best psychometric properties and add specific questions for RGND, (3) to validate the core PROM (CoPROM) set for RGND, and (4) to pilot the CoPROM set in research and clinical care for individuals with RGND.

Methods: We will use a mixed method design; (1) CoPRO set: Identifying common PROs measured in clinical trials and core outcome sets (review) and perform a qualitative study on the relevant PROs for individuals with RGND and their caregivers (focus groups and interviews). Eventually, reaching consensus on the most important PROs for RGND (Delphi survey and consensus meeting). (2) CoPROM set: Identifying and selecting PROMs with good psychometric qualities measuring the selected CoPRO set (review). (3) Subsequently, validate the CoPROM set for the RGND population. (4) Implementation of the CoPROM set at collaborating clinics.

Results: N.A.

Conclusion: With the identification of relevant PROs and the development of a core PROM set, we hope to optimize personalized care and research for the complex and vulnerable patient population with RGND.

Keywords: Rare genetic neurodevelopmental disorders, patient reported outcomes (PROs), patient reported outcome measures (PROMs)

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POSTER 16: Autism Spectrum Disorder (ASD), Obesity Type 1, Borderline Intellectual Functioning and KANSL 1 Sequence Variation: A Case of Koolen de Vries Syndrome (KdVs) in an Adult Male Person

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Background: KdVs may arise from intragenic heterozygous variants of KANSL 1, leading to haploinsufficiency of the gene or from 17q21.31 microdeletion encompassing the KANSL 1 gene. Clinically the KdVs is associated with facial dysmorphic features, hypotonia from birth onwards, leading to delayed motor development, cardiac defects, seizures, cryptorchidism, intellectual disability, autism spectrum disorders symptoms, friendly personal behavior.

Personal history: The patient, 32 years present age, was 3rd born by non-related parents. Neonatal hypotonia, bilateral cryptorchidism. Delayed language development, echolalia, and early motor hyperactivity. Selective feeding disorder and difficulties chewing solid food until 6 yrs. Learning disability and communication difficulties in primary school. He obtained a professional school diploma and now is working in a sheltered department. Systolic arterial hypertension has been documented since the 20 yrs of age. Mitral prolapse at echocardiography. Brain MRI and EEG are substantially normal. At thirty, acute thrombosis of the left subclavian vein.

Clinical examination: Height 180 cm, weight 102 Kg, CC 60 cm, BMI 31.48 (obesity class 1). Minor facial dysmorphic features (long face, flat mouth, bulbous nose), ichthyotic skin, numerous melanocytic nevi. Left-handed, mild motor clumsiness, hand tremors, bilateral nystagmus. Language characterized by grammar phrases, short and simple, reduced vocabulary.

Neuropsychological evaluation: Audiometry, BAEP, and VEP: normal. Brain MRI: normal. WAIS-III FSIQ = 81; VIQ = 79; PIQ = 85. At six years WIPPSI IQ =70 (VIQ=68, PIQ = 72). Token test: good capacities of seriation and discrimination. DSM5 criteria: ASD level 2. VASP: autonomy and adaptive capacity deficiencies. SCQ: 19/40 Aman Sing Rating Scale: marked irritability, low frustration tolerance, verbal aggressivity.

Genetic evaluation: Molecular analysis FMR 1: negative. Array CGH: normal. Targeted resequencing using Focused Exome (Sure Select QXT; Agilent) and direct (Sanger sequencing), documented a heterozygous variation of exome 2 in the KANSL1 gene:
g.21642_21643 delTT (NG_032784.1)
c.985_986delTT (NM_001193466.2)
p.Leu329Glufs*22 (NP_001180395.1)

Conclusions: Borderline intellectual disability, autism spectrum disorders and obesity may be associated with KdVs. This person has been treated for many years for behavioral difficulties which were considered reactive to the family conflicts. Finally, the parents divorced. The correct diagnosis was reached only when the genetic investigations became available.

Keywords: Koolen DeVries syndrome, ASD, obesity

POSTER 17: A Qualitative Exploration of Parents' Views About Wearable Devices for Research and Treatment Monitoring of Children with Genetic Neurodevelopmental Disorders

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Background: Wearable devices are useful tools for the measurement of neurological symptoms in individuals with neurodevelopmental disorders (NDDs). These can relay real-time data and provide objective and reproducible measurements without instruction-based protocols. A better understanding of the opinions of parents of children with NDDs is required to ensure that wearables are sensitive to the unique needs of this group. This qualitative study aimed to explore the experiences and views of parents regarding the use of wearable devices in clinical and research settings.

Methods: Semi-structured interviews were conducted with parents (n=12) of children with genetic NDDs. The inclusion criteria were parents with at least one child with a diagnosis of Fragile X, Prader-Willi, or Angelman syndromes, who had previous experience with a research study involving a wearable device. Codebook thematic analysis was used to systematically code and identify patterns across the transcribed dataset. These patterns were developed into themes to answer the research questions.

Results: Three main themes were identified. First, parents placed high value on the ease with which new technology could be incorporated into their pre-existent routine. Factors that incentivised parents to uptake wearable devices included feasibility, non-invasiveness, and the ability for use in the home. Second, parents' decision-making processes involved reflection on both positive and negative experiences in healthcare and research. Third, due to the specific, functional, sensory and behavioural features of the cohort, there is high value in open dialogue between parents and researchers in the early design and rollout phases of new technology.

Conclusions: There are unique factors associated with the behavioural phenotypes of children that impact likely uptake and success of wearable devices in the NDD population. A shared decision-making approach between researchers and parents is likely to facilitate the use of wearable devices for children who have genetic neurodevelopmental disorders.

Keywords: Genetic neurodevelopmental disorders, wearable devices, wearable technology, outcome measures, shared decision-making

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POSTER 18: IMAGINE -ID: Does Psycho-Social Support Predict Parental Mental Health Outcomes?

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Background: IMAGINE-ID is a national UK study of children with intellectual disability (ID) of known genetic origin. They are far more likely to experience mental health difficulties compared to their neurotypical peers, yet many caregivers have difficulty accessing appropriate care from children's services. We aimed to investigate the relationship between parental reports of support received for their child and their own emotional and behavioural adjustment. We hypothesized that caregivers reporting lower levels of support would experience poorer mental health themselves.

Methods: 1965 CYP (4-19 years) were recruited nationally to IMAGINE-ID via NHS facilities. Caregivers completed an online interview, the Development and Wellbeing Assessment (DAWBA) which includes an 'Everyday Feelings Questionnaire' about parental mental health. Information is obtained about their CYP's emotional and behavioural adjustment, and support received in terms of help or advice from a potential range of 12 community, school, social- or healthcare services.

Results: Caregivers reported receiving support from an average of 5/12 services (SD=2.8) for their CYP's mental health issues. Paediatric (medical) services were consulted by the highest proportion (n=1482, 75%); a similar proportion consulted teachers (n=1417, 72%). Parental mental health was negatively correlated with the number of agencies accessed for support to their child ($p<.001$). A simple linear regression model predicted parental mental health based on number of support agencies accessed ($F(1,1963) = 109.1$, $p<.001$), $R2$ .053 ($ß=.229$, $p<.001$), but statistical significance was lost when a multiple linear regression model controlled for child characteristics (age, developmental level, sex), child difficulties and socioeconomic deprivation ($ß=.005$, $p=.8$).

Conclusions: Multiple factors appear to contribute to mental health difficulties in caregivers of CYP with ID. Future analyses need to disentangle their relative contributions and inform intervention development.

Keywords: Intellectual disability, mental health, community support

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POSTER 19: Using Eye Tracking to Examine Visual Social Attention in SYNGAP1-Related Intellectual Disability

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Background: *SYNGAP1*-related Intellectual Disability is a neurodevelopment condition caused by a mutation of the syngap gene. Autism is a prevalent feature of this condition, with a formal diagnosis reported in approximately half of all patients. Eye tracking has been extensively used to examine social attention in autism. However, despite the prevalence of autism in *SYNGAP1*, eye tracking has not yet been utilised in this population. We therefore set out to use eye tracking methods to characterise visual social attention in *SYNGAP1*.
Method: 24 individuals with *SYNGAP1* and 12 typically developing controls completed three passive viewing tasks (face scanning, pop-out and social preference) whilst their eye movements were recorded.
Results: We found that those with *SYNGAP1* looked at faces and in particular the eyes and the nose less than the typically developing controls. For the pop-out task, in which an array of objects were presented, one of which was a face, again those with *SYNGAP1* looked at the face less than the typically developing controls. They also made fewer fixations to the face stimulus. However, there was no differences in either looking time or fixation count, when the groups looked at side-by-side naturalistic scenes (one image was social and the other non-social) in the social preference task. Although those with *SYNGAP1* did look more at the social scenes than the non-social scenes.
Conclusion: This is the first study to examine visual social attention in a *SYNGAP1* population, and as such it offers important and novel insights into their social impairments. It not only demonstrates the feasibility of conducting eye tracking in those with *SYNGAP1* but also shows that this population potentially displays similar social attention differences to face stimuli as seen in idiopathic autism.

Keywords: SYNGAP1-related ID; Eye-tracking; Autism; Visual social attention

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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% of cases are caused by a de novo deletion (Knoll *et al.*, 1989). 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). 2-7% of cases are caused by uniparental disomy (UPD; Engel, 1993; Prasad & Wagstaff, 1997), where two copies of the paternal chromosome are inherited, 2-8% of cases are caused by a mutation in the UBE3A gene (Kishino, Lalande, & Wagstaff, 1997) and 2-5% of cases are caused by an imprinting centre defect (ICD; Bürger *et al.*, 1997). 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 evok ed 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 (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, prognatism, 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).

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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

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(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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Effie Pearson, Mary Heald and Chris Oliver

(Updated May 2022)

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, 2013; International Classification of Disorders [ICD] 11; World Health Organisation, 2018) 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 infexible patterns of behaviour and interests. In addition, both classifications 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, or genetic condition or environmental factor, or is associated with another neurodevelopmental, psychiatric or behavioural disorder. 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.

Associated conditions

There is a significant association between autism and a wide range of other developmental and genetic disorders including Tuberous Sclerosis and Fragile X (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 problems, the most common being sensory impairments, autoimmune disorders, and obesity, gastrointestinal, and sleep disorders (Rydzewska *et al.*, 2021). The overall prevalence of epilepsy is around 12% (Liu *et al.*, 2022) with rates being highest (at around 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 recent meta-analysis, based on cases diagnosed via clinical interview, reported an overall prevalence rate of 60% (Lugo Marin *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), (Arnett *et al.*, 2019). 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 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 (Ma *et al.*, 2021).

Environmental risk factors

Recent research has highlighted the impact of gene-environment interactions and a number of potential environmental risks has been identified (Hertz-Picciotto *et al.*, 2018). These include high maternal and paternal age; maternal health factors such as obesity or drugs 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. However, there is no evidence that MMR or other vaccines are a cause of autism.

Prevalence

Prevalence estimates of autism vary, both across and within countries. The most recent systematic review update, based on 71 studies (Zeidan *et al.*, 2021), 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 other studies now suggest that the apparent gender bias may be at least partly due to the fact that formal diagnostic criteria may fail to identify some autistic girls and women (Driver & Chester, 2021).

Physical Phenotype

There is no distinct physical phenotype although minor physical anomalies and dysmorphic features are common. There are also increased rates of chronic and acute medical problems across the life span (Bishop-Fitzpatrick & Rubenstein, 2019). Imaging studies have so far failed to identify any neurological anomalies that are either consistently associated with, or unique to autism (Hashem *et al.*, 2020).

Life expectancy/natural history

An increased risk of premature mortality in autism, especially among individuals of lower IQ, has been reported in a number of studies and is associated with a range of disorders of the nervous, circulatory, respiratory and digestive systems. Among autistic adults of average or above intellectual ability, premature mortality is significantly associated with suicide, particularly among females (Hirvikoski, *et al.*, 2020). Epilepsy is one of the most common causes of early death in individuals of low IQ (Hirvikoski, *et al.*, 2016).

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 remaining "minimally verbal". Although intellectual disability was once thought to be a common feature of autism, more recent research indicates that 60%-70% of autistic people are of at least average intellectual ability (Zeidan *et al.*, 2020).

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 IQ and severity of social and communication impairments, and the adequacy of educational, occupational and other support systems (Howlin, 2021; Lord *et al.*, 2022).

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 help 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; Lord *et al.*, 2022).

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Websites:

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

- www.nas.org.uk
- www.autistica.org.uk
- https://www.autismspeaks.org/

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

- info@SPARKforAutism.org
- iancommunity.org/cs/adults

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Patricia Howlin, Updated March 2022

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.

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 has become the most common cause of congenital deaf-blindness (after "other" and "unknown"). These difficulties are present due to missing or malformed semi-circular canals and otoliths. 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.

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, & Schmittel, 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. Due at least in part to sensory impairments, language development and communication may be severely delayed.

Useful websites/associations for more information

- www.chargesyndrome.org
  US CHARGE foundation
- www.chargesyndrome.org.uk
  UK support group
- www.chargesyndrome.org.nz
  Australasian support group
- www.cmich.edu/colleges/class/Psychology/charge
  CHARGE research lab focused on behaviour

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Timothy S. Hartshorne, May, 2019

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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, hypondontia, 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.

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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 of 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 valporate 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

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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-Onchyodysplasia", "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 proccupations 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

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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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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; Srivstava 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 (Srivstava 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 diffiuclties 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).

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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).

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). Neibuhr 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)

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). 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 (Neibuhr, 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. 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). Repetitive behaviours are generally less common in CdCS than inother 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

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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). 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) 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, 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/
- 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 syndome (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 triplicationopy 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 inbalanced genome are reported (Li, Zhu, 2022).

221coding, 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 associaton with leakaemia in children woth 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 (Sleegers 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 commin 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

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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 withdrawl from activites and up to 90% of people show language regression. Features can appear similar to catatonia including stereotypes, reduced voilition 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 anti-depressant and antipsychotic medication. Electro-convulsive therapy, steroids and intravenous immunoglobulins have been trialled with some sucess 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 symnptoms have been described prior to dementia onset.

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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 abiltiies 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 at *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).

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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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Foetal alcohol syndrome/ Alcohol related neurodevelopmental disorder

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, interneuruonal signaling deficits and damage to scaffolding proteins interfering with neural migration (18).

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). 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

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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 hetertopias (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

Despite the high prevalence of the disorder, there have been few actual randomised studies of behavioural interventions specific to a FASD population. Those that have been have been small scale. Whilst some benefits are noted much more work is required. A review by Chandresena recently looked at possible strategies including medical, educational and psychological (16). More recent work has focused on best practice though experience guidance being developed such as that for ADHD and FASD (26). The recognition that bespoke treatments are required continued to drive the development of intervention such as the use of environmental modification approaches or bespoke parenting interventions, yet the testing of these through an RCT process remains limited.

Useful websites /associations for more information

- www.nofas.co.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

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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 unnmethylated 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 prophodiesterase 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 Dunmowm 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 may have 46,XY/47,XXY mosaicism. Mosaic 47,XXY occurs because of an error in the division of the sex chromosomes in the zygote after fertilization.

Incidence/prevalence

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

However, prenatal 47,XXY diagnoses 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. 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 to alleviate feminization effects that may have occurred due to insufficient testosterone levels, while also promoting the development of secondary male sexual characteristics. Other areas of increased risk developing over adulthood include low energy and libido, osteoporosis, thromboembolic disease, obesity, and diabetes mellitus. 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 have also been shown to decrease anxiety and increase motor proficiency (Samango-Sprouse *et al.* 2013; 2015). Individuals with a mosaic form are often less affected and may have normal fertility.

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 problems than the untreated child or the child postnatally diagnosed (Samango-Sprouse *et al.*, 2015, 2021). School-aged children frequently show problems with anxiety and mood dysregulation, self-esteem, and socialization. Socialization problems

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frequently relate to inhibition and anxiety, and they may become more pronounced during adolescence especially without hormonal treatment. Some of these problems may originate from frustration stemming from a relatively low 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 (Giedd *et al.*, 2007). Studies on boys with 47,XXY 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 to manifest as the dyspraxia and oral motor dysfunction that is often found in 47,XXY 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 (Samango-Sprouse and Law, 2001; Savic, 2012). Many 47,XXY males have normal or above average cognitive capacity with typically higher nonverbal IQs and lower Verbal IQs .

These neuroanatomical findings in 47,XXY 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 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 normalization after hormonal treatment therapy.

Available guidelines for behavioral assessments/ treatment/management

Once the individual or fetus is diagnosed with 47,XXY, it is important to seek consultation with medical professionals and health care professionals who are familiar with 47,XXY 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 throughout early childhood when discrepancies or deficits are identified to enhance early 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. 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. Because of

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decreased muscle tonus and androgen deficiency, an active health style is 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 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)

Alternative names:
Historically, Lesch-Nyhan syndrome is the designated term for this disease. Lesch-Nyhan Disease (LND) and hypoxanthine-guanine phosphoribosyl transferase (HPRT, HGprt) deficiency are also used to describe this disease. In addition to the classic form of LND, Jinnah and others have characterized two variant forms of the disorder -- 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 is present is all three types of LND.

First description:
It is interesting that the first description of Lesch-Nyhan Disease may have been in the year 1267. Beck (Euro J of Ped Surg 1991) identified an original description of what may be LND when he uncovered cases of self-injury, gout, and mental retardation 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 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 by Dr. Nyhan, and his medical student, who published data in 1964 on two brothers with LND in the American Journal of Medicine 36, 561 –570. Nyhan followed up this first article with a second article in 1965, A familial disorder of uric acid metabolism and central nervous system function in J of Pediatrics, 257 – 263. Not only was Nyhan the first to describe the familial nature of the disease, he has devoted his career to the study and care of patients with a variety of metabolic disorders including LND.

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. 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 year 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!

Due to the nature and importance of the purine salvage pathway, it is entirely likely that numerous cell processes and cell lines function abnormally. Although this area of research is in its infancy, Dauphinot *et al.* using microarray analysis, recently suggested biological processes involving cell-division processes and metabolic and nucleic acid processes, are dysfunctional.

Incidence:
This is a rare disorder that has an accepted incidence of about 1:380,000.

Genetic aspects:
Lesch-Nyhan Disease (LND) is a rare X-linked, recessive genetic disorder of the purine salvage pathway and is associated with cognitive impairment, hyperuricemia, renal involvement as well as the hallmark symptom of severe and involuntary self-injurious behaviors. The movement disorder is best characterized as dystonia superimposed on hypotonia. Although LND is appropriately considered a metabolic disease involving the absence, or near absence of the enzyme HPRT, it is best thought of as a disorder of the basal ganglia. Understanding the neurological manifestations of this enzyme defect allows for a thorough understanding of the disorder and subsequent comprehensive management strategies.

There are probably a few thousand individuals with this disease in the world. The mutations are in the HPRT1 gene located on the long arm of the

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X chromosome. Remarkably, over 600 different mutations have been identified in different families (O'Neill and others). The product of the normal gene is the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT) which recycles purines from DNA and RNA. Because it is an X-linked recessive mutation, it ought to occur only in males, but there have been several documented cases in females – thought to be a consequence of events explained by the Lyon Hypothesis. 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. (Xanthine stone formation is due to dose specific issues of allopurinol.) Unfortunately, treatment of the elevated serum uric acid with allopurinol does not have an impact on the neurobehavioral manifestations of the disease.

Physical phenotype and the basal ganglia:
Among other deficits, patients with LND have reductions of dopamine in the basal ganglia and 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 clearly evident. 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 is known to be involved in the regulation of areas other than the motor circuits, including personality, cognition and emotion. Visser, Bar, and Jinnah have reviewed in depth the involvement of the basal ganglia in LND, and their paper started a frame-shift in our understanding of the neurological aspects of the disease.

Cognitive aspects:
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 mentally retarded 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 by 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.

Is there evidence to suggest that there is a greater degree of dysfunction of neurons in the basal ganglia than the cortex or the fibers that descend from the cortex? This is an interesting question that requires further study (Gottle *et al.*.

Behavioral aspects:
The behavioral phenotype of Lesch-Nyhan Disease, physical and emotional self-injury, including severe self-mutilation and aggressive behavior, are generally involuntary in nature. The self-injurious behavior is not under the patient's control nor does the patient desire it. These self-destructive behaviors 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 life-span. 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 injury him or herself using external surfaces, this pattern tends to continue throughout the life-span. If the self-injury involves oral cavity or biting, then this pattern will reoccur throughout the life-span. Forms of self-injury include eye-poking, head banging, fingers in wheelchair spokes, and extension of arms in

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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. Removal of teeth is often difficult for families (and healthcare providers) to accept, however the teeth, when not removed, can be destructive. 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; Goodman, *et al.*)

Treatment:

Allopurinol is used to lower the elevated serum uric acid. 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. Nyhan (personal communication) has suggested that further work needs to be performed to address this clinical issue. Certainly, by lowering serum uric acid with allopurinol, death due to chronic renal failure has become quite rare.

Treatment for the behavioral manifestations of LND is multi-modal and should include: 1) judicious use of protective devices, 2) utilization of a behavioral technique commonly referred to as selective ignoring with redirection of activities, and 3) occasional use of medications.

The use of medications for treating the behavioral 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 behaviors', either motor or behavioral. Selective ignoring is a methodology that is designed to extinguish self-destructive emotional or physical behavior in the LND patient. It requires the caretaker to ignore such behavior by the LND patient towards said caretaker so that the behavior 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 Lesch-Nyhan Disease self-injury far exceeds that associated with other developmental disabilities, and, of course, is a consequence of the neurotransmitter and cell function abnormalities characterizing the disorder. Although not all individuals with this condition demonstrate severe behavioral 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. Issues regarding removal of teeth is addressed above (See exceptions to the CMS standard: 482.13. (e) (6).)

Deep Brain Stimulation (DBS) has been tried in numerous patients worldwide with LND to decrease the degree of dystonia. In this procedure neurosurgeons place two stimulators in the basal ganglia, similar to 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.

Life expectancy:

Life expectancy is a difficult issue to address as the extent of the associated clinical conditions of Lesch-Nyhan Disease 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 as a

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consequence of an unexplained neurological event. Certainly, as the accompanying clinical conditions are managed a longer life expectancy can be anticipated.

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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.

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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 effect 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

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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

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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 chomosome 2q22-2q23 or by a de novo mutation of a gene within this region. In 2001, Cachuex *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 mosiacism 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 prognanthism. By adulthood, the nose has lengthened, has a convex profile and overhangs the philtrum. MWS specific information and growth charts are know available from: https://mowat-wilson.org/new-diagnosis/welcome-packet/ 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.

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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 registryfor 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) is thought to suppress tumour formation by regulating cell division. A high spontaneous mutation rate means that about half of all cases arise in unaffected families.

Incidence/prevalence
About 1 in 2,500 births.

Physical features
Physical manifestations of NF1 include café-au-lait spots, 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). Diagnosis of NF1 is normally made if two of the following physical manifestations are present – six or more café-au-lait spots, two or more neurofibromas, skinfold freckling, two or more Lisch nodules or a family history of NF1 (Ferner *et al.*, 2007).

Life expectancy
Depends on nature and severity of clinical features.

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 (Payne *et al.*, 2010; Huijbregts *et al.*, 2015; Koini *et al.*, 2017).

Behavioural characteristics
Many patients experience social and behavioural difficulties (Barton & North, 2004). These include communication difficulties and difficulties forming and maintaining friendships. More than half of children with NF1 show significant scholastic difficulties and more than 30% meet criteria for ADHD. NF1 appears to be even more strongly associated with autism spectrum disorders, with prevalence rates up to 60% (Garg *et al.*, 2013). Cognitive deficits partly underlie the social dysfunctioning observed in NF1 (Huijbregts & De Sonneville, 2011).

Cognitive characteristics
The global intellectual abilities of individuals with NF1 fall within a normal distribution, albeit towards the lower end of this distribution. In addition, there are high rates of specific neuropsychological deficits including language, visuo-spatial, attentional, organizational and other executive deficits (Rowbotham *et al.*, 2009).

Treatment
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). 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 genetically heterogeneous disorder, with different causative mutations in the RAS-MAPK pathway. Syndromes with shared pathogenetic mechanisms and clinical overlap with NS include Cardiofaciocutaneous (CFC) syndrome, Costello syndrome (CS), Legius syndrome (LS), Neurofibromatosis type 1 (NF1), Noonan syndrome with multiple lentigines (NS-ML; formerly called LEOPARD syndrome), and Noonan syndrome-like disorder with loose anagen hair (NS-LAH). They are grouped into the neurocardiofacialcutaneous syndrome family, or the 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 caused by a pathogenic variant in LZTR1 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 16 other genes of the RAS-MAPK pathway are associated with NS and closely related disorders: SOS1 (10-13% of the cases), RAF1 (5-10%), RIT1 (5%), KRAS, NRAS, MRAS, BRAF, SHOC2, CBL, SOS2, RRAS, RASA2, MAP2K1, MAP2K2, LZTR1, and PPP1CB. In about 20 to 30% of the patients with a clinical diagnosis of NS, no mutation can be found yet (Allanson & Roberts, 2019; Grant *et al.*, 2018; Liao & Mehta, 2019; Motta *et al.*, 2020). Apart from these, preliminary evidence points at several other candidate genes such as RREB1 (Grant *et al.*, 2018; Kent *et al.*, 2020).

Incidence/prevalence

The incidence of NS is estimated between 1 in 1000 to 1 in 2500 live births (Allanson, 2010).

Physical features and natural history

Key characteristics are 1) short stature, 2) typical facial dysmorphology (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 dysplasia, cryptorchidism, ocular abnormalities, widely spaced nipples, and a webbed neck. However, these characteristics are not seen in all patients with NS, phenotypical expression is highly variable and often milder in adulthood than in youth (Allanson & Roberts, 2019; Noonan, 2005). The diagnosis is primarily made on clinical grounds, by observation of cardinal features. 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). 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.

Behavioural characteristics and psychopathology

A distinctive pattern of behavioural characteristics can not be recognised, although there are indications for an increased risk for behavioural problems in children, mostly characterised by social problems

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(e.g., social immaturity, diminished insight in social situations, impaired social skills), attentional problems, hyperactivity, and impulsivity (Pierpont, 2016; Pierpont *et al.*, 2018; Wingbermühle *et al.*, 2012a). Autism spectrum traits and ADHD symptoms seem to be more frequent than in the general population (Pierpont, 2016). There are indications that mood and anxiety problems, emotion regulation difficulties, and social distress are more common in children and adults with Noonan syndrome (Alfieri *et al.*, 2021; McNeill *et al.*, 2019; Pierpont 2016; Wingbermühle *et al.*, 2012a). Higher levels of introversion and alexithymia (problems in the identification and verbalisation of own emotions) in adults with NS are thought to contribute to internalising symptomatology (Roelofs *et al.*, 2019).

Neuropsychological characteristics

Neuropsychological findings show intelligence scores in a wide range, with a mildly lowered average intelligence. Language and motor development are often delayed. In children, a highly variable cognitive profile has been found, with indications for impairments in visual processing and language development, varying reports of memory problems, attention problems, and suboptimal planning and organisational skills (Pierpont 2016). These cognitive impairments might explain the anecdotally reported learning problems and need for special education. While cognitive problems are frequently present in childhood, cognition in adults with NS is mainly characterised by a lowered speed of information processing. As described above, social cognitive functions (recognising and expressing emotions) may be impaired as well (Wingbermühle *et al.*, 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 individual clinical and neuropsychological assessment is advised throughout the lifespan, especially at crucial moments in the development and when problems occur. 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).

More information

- 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.
- rasopathiesnet.org/wp-content/uploads/2014/01/265_Noonan_Guidelines.pdf For the Noonan Syndrome Clinical Management Guidelines.

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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; Reierson 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.

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 IPW being the genes whose absence of expression at the locus 15q11-13 are considered central to PWS. As yet, no single gene mutation has been identified as a cause of PWS, other than a mutation of the imprinting centre which itself influences the expression of several genes.

Despite significant advances in genetic testing, diagnosis is usually made clinically, and can be delayed until later in childhood. 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 29,000 and the prevalence is 1 in 52,000 (Whittington *et al.* 2001).

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).

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 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).

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 moods 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 aetiologic 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.

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).

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.

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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).

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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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

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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.

FOXG1 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, & Prechtl, 2005; Marschik *et al.*, 2014; Marschik *et al.*, 2013). Developmental regression in RTT remains still

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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

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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. Furthemore, fundamental RTT reserach 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 RTTor 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.rettsyndrome.org
- http://www.rettsyndrome.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 genetic alteration; 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; Dobreva 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

The true prevalence of SAS is unknown. However, 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).

Physical features and natural history

The major features of SAS have been incorporated into a S.A.T.B.2 diagnostic acronym; *S*evere speech anomalies, *A*bnormalities of the palate, *T*eeth anomalies, *B*ehavioural difficulties, with or without bone anomalies and/or brain defects, and age of onset below 2 years of age (Zarate & Fish, 2017).

Minor facial dysmorphisms have been described in individuals with SAS, including a thin upper lip, flat philtrum (grove 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 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 (Kikuiri 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 are common during infancy and into early childhood and have been attributed to the combination of craniofacial abnormalities and hypotonia (low muscle tone). 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 abnormal bone mineralisation (Mouillé et al., 2022; Zarate et al., 2018). Individuals may experience difficulties with movement and balance (Zarate & Fish, 2017; Zarate et al., 2017). 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 some individuals with SAS; however, 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 diagnostic acronym (Zarate & Fish, 2017; Zarate et al., 2017). High rates of self-injury (43%), property destruction (49%) and aggression (77%) are reported (Bissell et al., 2022). 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

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disorders (Cotton et al., 2020; Kumar & Zarate, 2020; Zarate et al., 2021).

Atypical sensory sensitivity 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 reports of an atypically 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

Limited genotype-phenotype correlations for SATB2 alterations have been established. However, in addition to core features of SAS such as developmental delay, behavioural characteristics, and craniofacial characteristics, individuals with large deletions are reported to evidence some specific characteristics. These include more frequent reports of a history of delayed growth (Zarate et al., 2019; Zarate et al., 2021), genitourinary anomalies (Zarate & Fish 2017), increased risk for cardiac defects (Zarate & Fish, 2017; Zarate et al., 2021), electrodermal changes such as thin skin or reduced subcutaneous fat (Zarate et al., 2021), and variable facial dysmorphism (Zarate & Fish, 2017).

A significantly higher proportion of individuals with disruptive pathogenic variants and missense variants have been reported to have sialorrhea (drooling/excessive salivation) (Zarate et al., 2019).

Zarate et al. (2019) report that individuals with large chromosomal deletions received a diagnosis of SAS at a significantly younger age (mean diagnosis age of 2.5 years) compared to individuals with a disruptive mutation, intragenic deletion, or missense mutation (mean diagnosis age of 8.3 years, 7.6 years, and 7.8 years, respectively).

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 Gene Foundation Australia: www.satb2.org.au

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Triple-X Syndrome (47,XXX; TXS)

First description and alternative names

In 1959 Jacobs (Jacobs et al., 1959) first described triple-X syndrome (TXS) in an infertile patient. The term "super female" is considered controversial and the term triplo-X syndrome is old fashioned. The terms triple-X syndrome, trisomy-X syndrome and 47,XXX syndrome are generally preferred.

After the first description there was a period of research in biased populations, e.g., in institutes for mentally retarded, asylums and forensic psychiatric hospitals (Olanders, 1975). In 1974 it was decided to screen 200,000 newborns for chromosomal disorders in several hospitals. TXS 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). Recent studies from other research groups published data from biased groups of cases (Wilson et al., 2019). Other studies reported results of mixed sex groups of participants and mixed groups of sex chromosome trisomies (47,XXX, 47,XXY, and 47,XYY). Some of the 47,XXY cases have received testosterone treatment, and others did not (Bouw, Swaab, Tartaglia, et al., 2022). These issues should be considered in the appraisal of study results.

Genetics and molecular biology

In TXS, there is an extra X chromosome in all cells or, in mosaic cases, in almost all cells. Most of the cases are diagnosed through prenatal diagnostic examinations. 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 lionization. The extra X chromosome in TXS is also silenced. In 46,XX females one-third of the genes on the X chromosome escape silencing (Migeon, 2007), and diverse patterns of X chromosome regulation have been shown during development, and 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 46,XX women. In TXS, there is another late-replicating chromosome, so replication time increases during each cell division (Barlow, 1973). The extra X chromosome also influences the nuclear architecture and epigenetic processes (Jowhar et al., 2018; Kelkar & Deobagkar, 2010). Whether incomplete silencing of the extra X chromosome, the prolonged cell cycle during division or epigenetic phenomena are relevant during development in 47,XXX, requires further research (Wainer-Katsir & Linial, 2019). Knowledge about sex differences in the brain (Raznahan & Disteche, 2021) and modern technology (Tallaksen et al., 2023) may help elucidate the biological relationship between the extra X chromosome and behavioural patterns in TXS.

Incidence/prevalence

1/1000 females have an extra X chromosome (Otter et al., 2010).

Physical features and natural history

Tartaglia et al. (Tartaglia et al., 2010) reviewed the physical findings in TXS. Since most of these findings (such as clinodactyly, epicanthal folds or hypertelorism) are minor physical features, the majority of 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 is probably the most important common feature (Patwardhan et al., 2002; Ratcliffe et al., 1994). 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 TXS have been reported, most of which do not exceeding the population prevalence numbers. But there are some disorders that seem to be more common in TXS: urogenital anomalies, (partial) epilepsy and Premature Ovarian Failure (POF) and infertility (Tartaglia et al., 2010). A recent Danish database study using clinical diagnoses

and medication use in women with TXS, 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

Low self-esteem seems to be the most common psychological feature in TXS (Freilinger et al., 2018; Otter et al., 2010). Social anxiety/shyness and executive dysfunction are common in TXS girls (Lenroot et al., 2014; van Rijn, Stockmann, Borghgraef, et al., 2014; van Rijn & Swaab, 2015). Social cognitive problems are common in TXS girls, probably due to language disorders (Bishop et al., 2011; Wilson et al., 2019). Developmental problems in language development have been described in TXS and in other sex chromosome trisomies as well, but the problems seem to be more severe in TXS girls (Capelli et al., 2022). Another study in TXS girls showed a developmental pattern that resembled the development of girls with autism with mild or late presenting autism symptoms (van Rijn, Stockmann, van Buggenhout, et al., 2014). Even in toddlers and very young children, problems in social communication and social interaction have been revealed (Bouw et al., 2023; Bouw, Swaab, Tartaglia, et al., 2022). Challenging behaviour may be the result of any of these developmental difficulties. However, early recognition of limitations in social functioning, in social cognitions and linguistic limitations may enable early intervention (Bouw, Swaab, & van Rijn, 2022). TXS girls living in a stable family function better than TXS girls in an unstable family (Netley, 1986). The TXS girls seem to be less able to cope in a stressful environment. After leaving school, most of the girls will find a job that reflects their non-verbal abilities (Robinson et al., 1990). Adults might face occupational problems (Attfield, 2021; Otter et al., 2012; Stochholm et al., 2013).

There seems to be a higher prevalence of psychiatric illness in general in TXS (van Rijn, 2019). 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 TXS do not experience major mental health problems (Freilinger et al. 2018). This was confirmed by a recent study in a larger group of adults with TXS (Otter, Campforts, Stumpel, van Amelsvoort, & Drukker, 2022). This study showed a higher prevalence of major depressive episodes (43.3%, psychotic disorders (29.4%), suicidality (23.5%) and higher 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, Campforts, Stumpel, van Amelsvoort, & Drukker, 2022). This Dutch study revealed no differences between women with TXS and controls in psychiatric medication use, which contrasts with the results of a Danish study, which revealed slightly higher levels psychiatric medication use, especially antipsychotics and medication used for ADHD (Berglund et al., 2022).

Scientific progress through neuroimaging findings

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).

A group from National Institute of Mental Health (A. Raznahan) published several papers on neuroimaging in sex chromosomal disorders. These studies revealed changes in cortical thickness and surface areas of the brain (Warling et al., 2020). These studies are of scientific importance, but until now, there is no clinical progress to be expected from neuroimaging in individual cases (Raznahan & Disteche, 2021) and the variability in the behavioural phenotype has not been explained (Otter, Campforts, Stumpel, van Amelsvoort, & Drukker, 2022).

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Neuropsychological characteristics

Data on intelligence in girls and adolescents are consistent, indicating that the full-scale IQ is almost 20 points lower in these girls than expected in the family (Robinson et al., 1990). Whether the girls show problems in reading or arithmetic is not uniformly reported in the case reports. Clinical experience suggests that some difficulties during arithmetic lessons result from language disorders. Mild or serious academic problems/special educational needs are common (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 or attention deficit disorder (ADD) (Lenroot et al., 2014)? Clinical experience treating ADD with medication suggests that the treatment is less effective than in 46,XX cases; however, controlled treatment studies are lacking (Leggett et al., 2010). A recent study in adults revealed that women with TXS score lower in general intellectual functioning and have impairments in motor processing speed and attention compared to controls, but do not differ with respect to executive functioning (Otter, Campforts, Stumpel, van Amelsvoort, Vingerhoets, et al., 2022). Women with TXS performed worse on an Emotion Recognition Task, particularly concerning recognising sadness, fear and disgust, so-called negative emotions (Otter et al., 2021).

Available guidelines for behavioural assessment/ treatment/management

There is no evidence-based management guideline, although Otter et al. have proposed a guideline of 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 since recent studies indicate language impairments in children (Bishop et al., 2018; Capelli et al., 2022), social-behavioural problems in children (Wilson et al., 2019) and adults (Otter et al., 2021), and neurocognitive problems in children (Urbanus et al., 2020) and adults (Otter, Campforts, Stumpel, van Amelsvoort, Vingerhoets, et al., 2022). 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

- The Dutch parents' support website: http://triple-x-syndroom.nl/. This website shows many links to scientific papers and useful links, e.g., links to international chat pages for parents and TXS girls/women. Scientific papers and syndrome sheets are available in several languages: English, French, Spanish, German and Dutch.
- Unique, a parents support group from the United Kingdom provides a syndrome sheet with information on physical and behavioural developmental issues: https://www.rarechromo.org/media/information/Chromosome_X/Triple_X_syndrome%20Trisomy_X%20FTNW.pdf ; 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 and 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 active in fundraising for the support of 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 SEGA (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, SEGA 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; Leclezio 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.tsalliance.org
  [USA user/carer organization]
- www.tscinternational.org
  [International user/carer organization]
- www.tscinternational.org
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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.

Genetics and molecular biology

In humans, partial or complete loss of either of the sex chromosomes results in the condition. A phenotype arises because of haploinsufficiency for genes that are normally expressed from both X- chromosomes in females (or from the X and Y in males). Early degeneration of the ovaries leads to oestrogen insufficiency. We now know the genetic sequence of the X chromosome but this has not led to the identification of susceptibility genes; so far, the only 'Turner' gene identified (SHOX), influences growth in stature.

Incidence and prevalence

The prevalence of the syndrome is 4 per 10,000 live female births. Whilst this is the most common chromosomal aneuploidy, the vast majority of affected conceptuses (95% or so) are spontaneously aborted. In ~70% of X-monosomy, there is loss of all or part of the paternal sex chromosome; the single normal X is maternal in origin. In 50% of all clinically identified Turner syndrome there is more than one obvious cell line. One is usually monosomic, the other contains either the full complement of 46 chromosomes, or some other complex structural variation. These so-called mosaics may have either a more mild, or a more severe, phenotype than X-monosomy, depending on the genetic abnormality. A minority of females with X-monosomy may never be clinically identified, especially if they have a mild phenotype.

Physical features and natural history

There are many possible physical characteristics of the syndrome, but none is invariable. If the condition is not detected at birth (usually suspected because of a transient edema maximal over the lower legs and feet, which rapidly clears) the diagnosis may not be made until middle childhood. The usual reason for ascertainment 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 and a slight ptosis. The chest is typically broad, with widely spaced breasts. When standing with her arms at her 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.

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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 is then lacking, and secondary sexual characteristics may be delayed until promoted by endocrinological management (oestrogen supplementation). Physical immaturity can be associated with difficulties integrating with a typical peer group during early adolescence, but the most important contributory influence is the associated deficits in social cognitive competence. These are related to abnormal development of the 'social brain', and are severe in at least 30% of cases. Consequently, forming and maintaining peer relationships is often problematic, especially as these become more complex during later adolescence. As adults, many women with Turner syndrome cannot function effectively in complex social work environments, and a substantial minority chooses to take jobs focused on child-care (especially nursery nursing, in the UK). This choice is not motivated by their (usual) infertility but by their subtle and superficially mild autistic symptomatology. The acknowledgement that a substantial minority of females with the syndrome have both the social and other features of an autism spectrum disorder (such as cognitive rigidity) is rarely appreciated by the paediatricians or endocrinologists who manage the syndrome in childhood and adulthood.

Many females with Turner syndrome have poor self-esteem, especially in later life. This is largely due to their difficulty in establishing satisfactory social relationships, for a variety of reasons including the social-cognitive difficulties. Their social problems are compounded by hearing loss, which needs to be identified and treated early. There is virtually no evidence that their social adjustment issues are due to short stature or infertility. They will not be resolved by growth-hormone treatment, although this may have other benefits. In the United Kingdom, and increasingly in Europe, there is an acknowledgement among Turner syndrome support groups that the symptoms of a mild autism spectrum disorder (ASD) are common and that they impact on friendships and family relationships. As in idiopathic ASD, there is often an association with anxiety, especially social anxiety.

Neuropsychological characteristics

Almost all have normal verbal intelligence. About 80% have relatively poor visuospatial memory (approx. 1 SD below norms), and 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 numerical magnitude.

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 have idiopathic ASD, 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.

Available guidelines for behavioural assessment/ treatment/management

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- 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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David H Skuse, 2014

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 Sedlačková 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 Sedlačková'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, Sedlačková 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 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 multisystemetic impact of 22q11.2DS, it is important that each individual has an individualised care plan involving a multidisiplinary 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 occuring 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

Williams Syndrome (also known as Williams-Beuren Syndrome)

First descriptions:
The syndrome was first described by Williams *et al.* (1961) in four patients with supravalvular 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 Morris, 2017 for review). 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 (Morris, 2017).

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 Morris (2017). 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 supravalvular 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 (Fisher *et al.*, 2016) 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 Martens *et al.*, 2008; Skwerer & Tager-Flusberg, 2011; Royston *et al.*, 2019 for reviews); pragmatic language difficulties may also become more apparent with age (Van Den Heuvel *et al.*, 2016). Adaptive behaviour skills are often relatively poor (Howlin *et al.*, 2010) but research findings on the

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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 (oppositionality 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 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; Stinton *et al.*, 2010; 2012)

Further information

- www.williams-syndrome.org.uk

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Patricia Howlin, 2014
Patricia Howlin, Updated 2019

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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 clinical manifestations. 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 ethiology. The high variability present at both clinical and molecular level can cause difficulties in diagnosis of WHS.

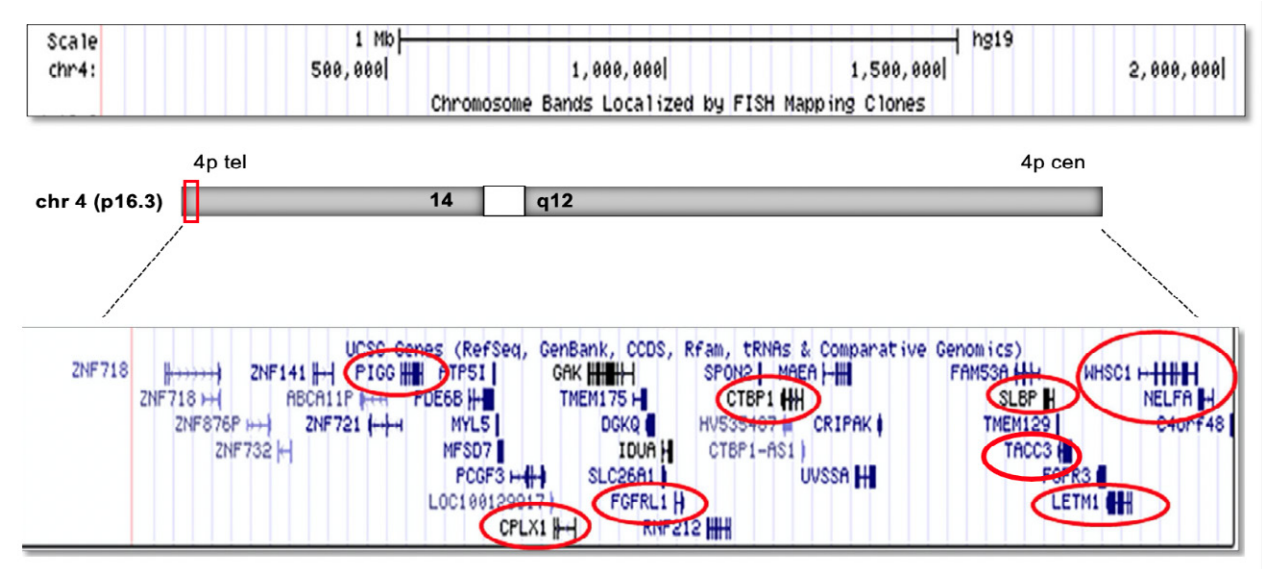

Figure 1. Diagram showing the distal region of chromosome 4p, where candidate genes for seizures and craniofacial features map (LEMT1 and WHSC1; Zollino *et al.*, 2003; Rodrıguez *et al.*, 2005). [Diagram was modified from Battaglia *et al.*, 2015].

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The genotype often arises from an unbalanced translocation event (t4;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%). 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.

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.

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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, Behavioral 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. Children with WHS are more severely impacted (~ 65% are profoundly ID) in both general cognitive ability and overall adaptive behavior 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 behavior, children with WHS exhibit relative competence in socialization skills compared to their abilities in other adaptive behavior 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).

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.

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Gene Fisch 2014. Updated in 2022 by Flora Tassone

47,XYY Syndrome

First description and molecular biology

47,XYY; XYY syndrome; YY 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; a few cases resulting in an additional Y chromosome. In some cases, it arises during early embryogenesis in a post-zygotic 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, 47,XYY may be increasingly detected prenatally through non-invasive prenatal screening (NIPS). This screening should be confirmed prenatally (amniocentesis or chorionic villus sampling) or postnatally (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 abnormalities of chromosome numbers to provide a definitive diagnosis.

Physical features and natural history

Physical phenotypic differences associated with XYY syndrome are usually mild. Hypertelorism,(small h) macrodontia, pes planus, central adiposity, clinodactyly, larger head circumference than typically developing boys have been described (Bardsley *et al.*, 2013; Lalatta *et al.*, 2012). Speech delay is common. Delayed development of motor skills (such as sitting and walking), weak muscle tone (hypotonia), and behavioral and emotional difficulties are also frequent. Boys have increased growth velocity during childhood, and adult height is usually increased approximately 7cm (3") above what is expected (Aksglaede *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 XYY than in the general population (Bardsley *et al.*, 2013).

Puberty, testicular function, and fertility are usually normal (only a trend to macroorchidism has been signaled in early puberty), whereas boys with Klinefelter syndrome (KS) experience testicular failure.

Behavioral and psychiatric characteristics

Individuals with XYY syndrome may be at increased risk for behavioral problems and psychiatric disorders. There is an increased rate of diagnosis of attention deficit hyperactivity disorder (ADHD) [more marked than in 47,XXY (KS)], and increased risk of problems with distractibility, impulsivity, difficulties with temper management. Problems with social relatedness are also common. Individuals with 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 XYY.

Prenatal diagnosis was associated with higher cognitive function and less likelihood of an ASD diagnosis (Ross *et al.*, 2015). Further, expression of NLGN4Y, a gene that may be involved in synaptic function, is increased in boys with XYY when compared to the neurotypical XY controls (Ross *et al.*, 2015). Psychiatric diagnoses are more common in

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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,XXY (Verri *et al.*, 2008).

Since the discovery of the 47,XYY karyotype, many studies have focused the relationship between a 47,XYY karyotype, aggressiveness, and deviance—attempting to associate this syndrome with criminal and deviant behavior. These studies, however, never reached statistical significance, and may be quite representative of the population due to selection bias.

Neuropsychological and neurological characteristics

47, XYY syndrome is usually associated with normal to slightly diminished cognitive function as measured with IQ; verbal IQ may be more affected than performance IQ. Many boys require speech therapy in their early years, as they may exhibit speech delay. Learning disabilities have been reported in about 50% of cases, with reading particularly affected. Difficulties with attention and impulse control are frequently reported.

Voxel-based morphology (VBM) revealed that boys with 47,XYY 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,XYY boys. VBM also found extensive WM modifications bilaterally in the frontal and superior parietal loves in 47,XYY 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 characterized in the 47,XYY 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 gray and white matter is reduced in males with XYY, 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 XXY. The patterns of regional gray matter and white matter variation in XYY boys are associated with deficits in motor and language abilities (Bryant *et al.*, 2012). These studies further link brain development, behavior, 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,XYY syndrome is associated to higher risk for seizures, focal epilepsy, and an electroclinical pattern characterized by focal spike and waves (similar to benign focal epilepsy) has been described in 47,XYY boys (Torniero, 2010). Males with 47,XYY show increased total gray matter (GM) and white matter (WM) volume when compared to 46,XY and 47,XXY males (Bryant, 2012). Increased grey matter may be the result of reduced synaptic pruning, leading to altered synaptic function and perhaps increased seizure risk (Bardsley, 2013).

Available guidelines of behavioral assessment/ treatment/management

Once 47,XYY 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 sensorimotor approach. In the school setting, assistance from special educators or individualized education programs (IEPs) may benefit the child.

Behavioral therapy or medication for boys may be prescribed for 47,XYY boys with ADHD and/or behavioral problems. In some cases, acne treatment may be beneficial in boosting self-confidence. Hormonal therapy may be also recommended to supplement development and growth.

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Useful websites/associations for more information

- The Association for X and Y Chromosome Variations (AXYS) https://genetic.org/variations/about-xyy/
- The Focus Foundation http://thefocusfoundation.org/x-y-chromosomal-variations/xyy/
- Genetics Home Reference https://ghr.nlm.nih.gov/condition/47xyy-syndrome
- Genetic and Rare Diseases (GARD) Information Center https://rarediseases.info.nih.gov/diseases/5674/47-xyy-syndrome#ref_9860
- National Organization for Rare Disorders (NORD) https://rarediseases.org/rare-diseases/xyy-syndrome/

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The 26th SSBP International Research Symposium

Educational Day: 5th September 2024 • Research Symposium 6th – 7th September 2024 • Bali, Indonesia

Early identification and treatment of genetic and neurodevelopmental disorders

The Society for the Study of Behavioural Phenotypes will be holding their 26th International Research Symposium, in Bali, Indonesia on the 6th and 7th September 2024. The Educational Day will be held on 5th September. The theme will be: Early identification and treatment of genetic and neurodevelopmental disorders.

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