24th SSBP International Research Symposium

Programme Book

8th – 10th September 2022 • Oslo, Norway

Save the date!

25th SSBP International Research Symposium will be held virtually 14th–15th September 2023

Abstract submission opens: 1st April 2023
Registration opens: 1st May 2023
Deadline for online abstract submission: 20th May 2023
Deadline for discounted early bird registration: Friday 18th August 2023

A series of Educational Webinars will be held during the year
Research Symposium: 9th–10th September 2023

Join us online for our 25th Research symposium, the theme will be *Expanding a Global Perspective on Behavioural Phenotypes*

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

8th– 10th September 2022

The 24th SSBP International Research Symposium

Developmental Disorders and Behavioural Phenotypes Across the Lifespan

Oslo, Norway

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Welcome from the Conference Organisers

We are delighted to welcome you to the 24th Society for the Study of Behavioural Phenotypes International Research Symposium and Educational Day, held in Oslo.

Oslo is the capital of Norway, and the home city of our King and Queen. Oslo is the economic and governmental centre of Norway, and was, in the early 2000s, one of the fastest growing European major cities. Just above 700 000 people live in Oslo today. Oslo is almost 1000 years old, and was founded in the Viking age.

The theme of this year's conference is Developmental Disorders and Behavioural Phenotypes across the Lifespan. The program highlights the contributions that population-based data make towards understanding behavioural phenotypes and the impact of aging on presentation. The Nordic countries are particularly suited for such research with their curated populations and patient's registries and biobanks, and possibilities to share data across sectors and countries. The Nordic countries have egalitarian, universal healthcare systems and generally high trust in government, enabling the very broad inclusion in research in these countries. The study of behavioural phenotypes needs multiple approaches, and cohort studies of how particular genotypes manifest with age will be presented.

We are happy that we finally can meet each other face-to-face from all over the globe.

We hope you enjoy your time at SSBP Oslo.

Terje Nærland, Heid E. Nag, Monica Stolen Dønnum and Anne Lise Høyland
Conference Coordinators

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Oslo Conference Organisers

Dr Terje Nærland

Terje Nærland is a Senior Scientist at the National centre for Neurodevelopmental disorders in Norway (NevSom) and Director of the K.G. Jebsen centre for Neurodevelopmental Disorders, a centre of excellence in translational medicine. The K.G. Jebsen centres objective is to investigate the variation in clinical presentation of rare disorders with a particular focus on autism spectrum disorders. Nærland is coordinating the activities across paediatrics, psychiatry, habilitation, and neurology departments with investigations from large populations and clinical samples.

Dr Heidi Nag

Heidi Elisabeth Nag has worked at Frambu Resource Centre for Rare Disorders as a special educational advisor since 2005. Frambu is one of nine centers for rare disorders in Norway and part of the National Advisory Unit on Rare Disorders in Norway. Heidi mainly works with and does research regarding rare disorders with neurodevelopmental disabilities and is especially interested in challenging behaviour and communication. In 2020 she finished her PhD in Educational Science with the topic: Behavioural Phenotypes of Smith-Magenis syndrome (SMS).

Dr Anne Lise Høyland

Anne Lise Høyland, MD, PhD, is chief of the Child and Adolescent Habilitation Unit at St.Olav's University Hospital in Trondheim, Norway. She is trained both as a Paediatrician and a Child and adolescent psychiatrist. Her interest has especially been on ASD with research both in electrophysiology and executive function and epidemiology.

Monica Stolen Dønnum

Monica Stolen Dønnum is a social educator with a master's degree in behaviour science from Oslo Metropolitan University. Monica works at Akershus University Health Trust, department of habilitation services for adults. She has worked for people with autism and intellectual disability for 20 years and has experience from different services.

Scientific Committee

Professor Patricia Howlin,
Emeritus Professor of Clinical Child Psychology,
Institute of Psychiatry Psychology and Neuroscience,
King's College, London.

Professor Anna Jansen
Division of Pediatric Neurology
Antwerp University Hospital
Belgium

Dr Heidi Elisabeth Nag
Special Educational Advisor, PhD
Frambu Resource Centre for Rare Disorders, Norway

Dr Ida Elken Sønderby
Department of Medical Genetics, Oslo University Hospital, Oslo, Norway
KG Jebsen Centre for Neurodevelopmental Disorders, University of Oslo, Oslo, Norway.
Norwegian Centre for Mental Disorders Research (NORMENT), Division of Mental Health and Addiction, Oslo University Hospital and University of Oslo, Oslo, Norway

Dr Attila Szabo, Ph.D.
Research Fellow
Norwegian Centre for Mental Disorders Research (NORMENT),
KG Jebsen Centre for Neurodevelopmental Disorders,
Institute of Clinical Medicine, University of Oslo

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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

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

Forthcoming Meetings of the SSBP

2023	Virtual	25th International

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
	Professor Flora ***Tassone*** (USA) – ftassone@ucdavis.edu
	Dr 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

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Tom Oppé and the Tom Oppé Distinguished Lecture

Tom Oppé

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

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

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

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

Tom Oppé Lecturers

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

2022 Tom Oppé Distinguished Lecturer: Professor Kevin Mitchell

Kevin Mitchell is Associate Professor of Genetics and Neuroscience at Trinity College Dublin. He studies the genetics of brain wiring and its relevance to variation in human faculties, neurodevelopmental disorders and perceptual conditions like synaesthesia.

His current research focuses on the biology of agency and the nature of genetic and neural information.

He is the author of "*INNATE – How the Wiring of Our Brains Shapes Who We Are*" (Princeton University Press, 2018), writes the *Wiring the Brain* blog and is on Twitter @WiringtheBrain. He is currently working on a new book, "*AGENTS - How Life Evolved the Power to Choose*", for Princeton University Press.

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

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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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 will be 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. 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 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 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.

The Leclezio-de Vries Lecturers

2022	The TAND Consortium
2019	Ms Siobhan Blackwell

2022 Pat Howlin and Leclezio de Vries Lecturer: **Stacey Bissell** on behalf of the **TAND Consortium**

The Tand Consortium

'Empowering families through technology: A mobile-health project to reduce the TAND identification and treatment gap (TANDem)' is funded by the King Baudouin Foundation with support from the Tuberous Sclerosis Association UK. This four-year international project aims to address the identification and treatment of TSC-Associated Neuropsychiatric Disorders (TAND). The project has three main objectives: 1) to develop a quantified, self-report TAND Checklist into a mobile app, 2) to develop consensus clinical guidelines for identification and treatment of TAND clusters integrated as a TAND toolkit within the mobile app, and 3) work as part of a global TAND Consortium (@TANDconsortium) to establish TAND expertise, capacity-building, public engagement and early career researcher initiatives.

Presented by Stacey Bissell

Dr Stacey Bissell is a Research Fellow and Assistant Professor at the School of Psychology, University of Birmingham. Her PhD Fellowship co-funded by the Tuberous Sclerosis Association UK and Cerebra, investigated behavioural, developmental and communication profiles in young children with tuberous sclerosis complex (TSC) under the supervision of Prof Chris Oliver and Dr Lucy Wilde, with a particular focus on TSC-associated neuropsychiatric disorders (TAND). Her current research uses direct observational sleep methodology to characterise putative associations between poor sleep, pain, mental health, social cognition and behaviour in neurodevelopmental disorders. In 2019, Dr Bissell was appointed Research Lead for the Eat/Sleep cluster of the 'Empowering Families through Technology: A mobile-health project to reduce the TAND identification and treatment gap (TANDem)' research project and is actively contributing to the development of TSC consensus behavioural guidelines as part of the TAND Consortium.

Sponsors

The SSBP is extremely grateful to the following organisations for their sponsorship of SSBP 2022 in Oslo.

Norwegian National Advisory Unit on
RARE DISORDERS

FRAMBU
RESOURCE CENTRE FOR RARE DISORDERS

LIVSVITENSKAP
LIFE SCIENCE

Oslo
University Hospital

NevSom – Norwegian Centre of Expertise for
Neurodevelopmental Disorders and Hypersomnias

Venues

1 Educational Day (8th September)

1 Research Symposium (9th-10th September)

The Educational Day and The Research Symposium will be held at:
Oslo Kongressenter
Youngs gate 21
0181 Oslo

t. +47 90 70 99 99

Rail travel 700m to the train station
Bus 800m to the bus terminal

2 Welcome Reception (8th September)

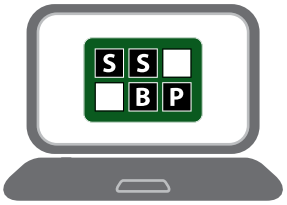
The Conference Reception will be held at:
Oslo Rådhus (Oslo City Hall).
Fridtjof Nansens plass,
Oslo
t. +47 21 80 21 80

1 Conference Dinner (9th September)

The Conference Dinner will be held at Oslo Kongressenter

E-Venues

SSBP Website
www.ssbp.org.uk



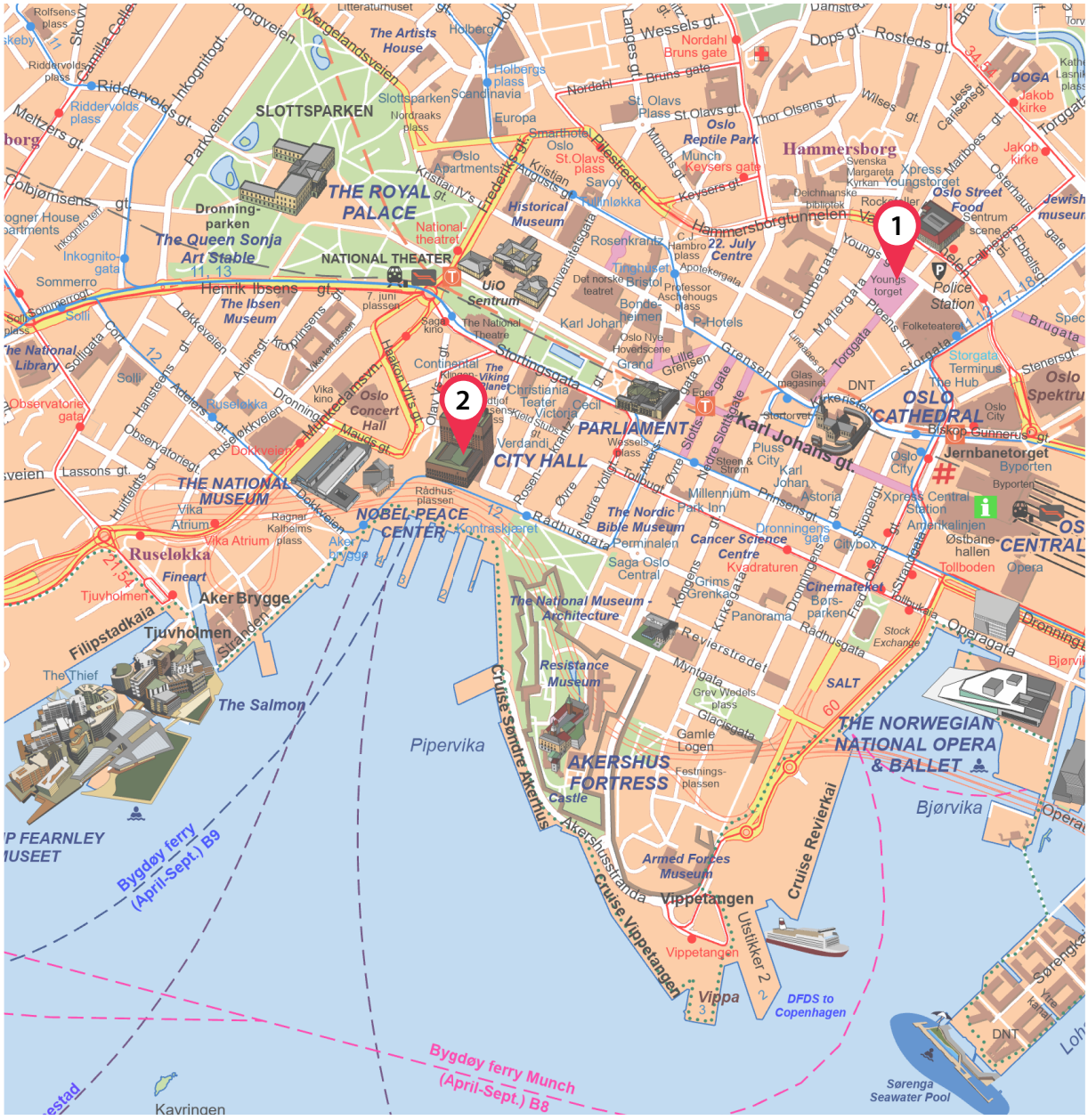
The SSBP Website is the central base for the virtual participants.

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 recordings will also be made available for 'catch-up viewing on the website.** We will endeavour to upload recordings as soon as possible.
- **Poster presentations will be made available on the website**.
- **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.

Map of conference areas in Oslo



Map © Visit Oslo

1 **Oslo Kongressenter**
Youngs gate 21
0181 Oslo

2 **Oslo Rådhus** (Oslo City Hall).
Fridtjof Nansens plass,
Oslo

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Keynote Speaker Profiles:

(In Alphabetical Order)

Professor Patricia Howlin

Patricia Howlin is Emeritus Professor of Clinical Child Psychology at the Institute of Psychiatry, Psychology and Neuroscience, King's College London. Her principal research interests focus on trajectories of development in individuals with autism and factors related to outcome. Professor Howlin is a Fellow of the British Psychological Society and Fellow of the international Society for Autism Research. She is President of the Society for the Study of Behavioural Phenotypes and past Chair of the UK Association of Child Psychology and Psychiatry. She is a founding editor of the journal "Autism" and author of over 200 research publications.

Professor Connie Kasari

Connie Kasari, Ph.D. *University of California, Los Angeles, Distinguished Professor of Human Development & Psychology in the School of Education with a joint appointment in the Department of Psychiatry*. She received her Ph.D. from the University of North Carolina at Chapel Hill and has been on the faculty at UCLA where she teaches both graduate and undergraduate courses and has been the primary advisor to more than 70 PhD students. She is a founding member of the Center for Autism Research and Treatment at UCLA. Her research aims to development novel, evidence-tested interventions implemented in community settings. Recent projects include targeted treatments for early social communication development in at risk infants, toddlers and preschoolers with autism, and peer relationships for school aged children with autism. She leads several large multi-site studies including a network on interventions for minimally verbal school aged children with ASD, and a network that aims to increase equity in access to interventions for children with ASD who are under-represented in research trials. She is the current president of the *International Society of Autism Research.*

Dr 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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Dr Ellen Melbye Langballe

PhD in psychology, Ellen Melbye Langballe, works at the Norwegian National Centre for Ageing and Health. She is the head of the ageing field and senior scientist.

Dr. Ida Elken Sønderby

Ida Elken Sønderby is a senior researcher in neurodevelopmental genetics and brain imaging at Oslo University Hospital, Department of Medical Genetics (https://ous-research.no/sonderby), Norway. She is associated with the Norwegian Centre for Mental Disorders Research (NORMENT) and the K.G. Jebsen Centre for neurodevelopmental disorders.

She obtained her PhD in Plant Molecular Biology at the University of Copenhagen and later worked with human sequencing and associations studies on schizophrenia in Norway. During a Marie Curie industrial stay at deCODE Genetics in Iceland in 2013, she developed a particular interest in copy number variant (CNVs), i.e. regions of the genome either deleted or duplicated. Together with Ole Andreassen, she started up the Enhancing Imaging Genetics through Meta-Analysis (ENIGMA-CNV) working group in 2015, a group that she still co-chairs. ENIGMA-CNV carries out mega-analysis and links structural MRI data with copy number variants (CNVs) in the human genome. Using CNVs as 'models', her goal is to improve the understanding of (neurodevelop)mental disorders and neurogenetic mechanisms shaping human behavior, cognition, and development.

Dr Kaja Selmer

Kaja Selmer, MD, PhD, is a senior scientist at the Division of Clinical Neuroscience, Oslo University Hospital (https://www.ous-research.no/selmer/) and head of section for the Neuroscience registry and Biobank. Her main research interest is the genetics and epigenetics of neurological disorders, with the aim of revealing disease etiology and development and its interplay with treatment and environmental factors.

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Professor David Skuse

David Skuse is Professor of Behavioural and Brain Sciences at the Institute of Child Health, University College London, and Honorary Consultant in Developmental Neuropsychiatry at Great Ormond Street Hospital for Children. He trained in academic psychiatry at the Institute of Psychiatry, London, before moving to the Institute of Child Health in 1985. He devised the computerized 3di interview for autism spectrum disorders, which is used by over 20 countries worldwide, many in translation and developed revised criteria for Autism Spectrum Disorders for the 11th Revision of the WHO's International Classification of Diseases.

Currently, his primary research program, funded by a UK Medical Research Council grant (2015-2025) is designed to identify mental health risks in children with intellectual disability due to rare genetic disorders. He is also co-investigating a European cohort of children in the largest study yet of Duchenne Muscular Dystrophy, which aims to discover whether gene therapy can ameliorate associated neurodevelopmental disorders such as autism. He also leads an investigation into the development of novel tools for autism assessment that are more suitable for use in ethnically diverse communities than current procedures, with a view to reducing waiting lists.

Professor Ann Swillen

Professor Ann Swillen is professor at the Departments of Human Genetics and Rehabilitation Sciences at KU Leuven (University of Leuven, Belgium) and Head of the Laboratory for Behaviour and Neurodevelopment (for more information please visit her lab's website.)

Trained as a clinical educational psychologist, Prof. Swillen works at the genetic clinic with children, adolescents and adults who have neurodevelopmental disorders such as intellectual disability (ID)/developmental delay (DD) and autism spectrum disorders (ASD). She has more than 30 years of experience/expertise in the clinical follow-up and research of individuals with Copy Number Variants (CNV's), including those with 22q11.2 deletions/duplications and other CNv's, resulting in >120 scientific papers on NDD in CNV's. **Ann** participates and takes leading positions in several rare disease networks including the NDD European Reference Network (ITHACA), MINDDS (co-PI), 22q11 IBBC (PI), G2MH-consortium (PI). She is co-author of international guidelines on 22q11 DS, Phelan-Mc Dermid syndrome (PMS) and wrote several chapters in international handbooks.

Since 1994, she coordinates the multidisciplinary clinic for persons with 22q11.2 DS at the university hospital (UZ Leuven), and since 2018 she co-started the multidisciplinary clinic for patients with PMS. She recently developed a psychoeducational tool for families www.geneticpuzzle.eu to improve understanding and communication around a CNV in the family. Ann received the Angelo DiGeorge Medal in 2016, and the Edelweiss Award in 2020.

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Dr Charlotte von der Lippe

Charlotte von der Lippe is a medical doctor (M.D.), with a specialty in clinical genetics. She also holds a Master of Science, and a PhD. Her current position is as a senior consultant in clinical genetics at the department of Medical Genetics at Telemark Hospital Trust. In addition to her clinical work, she supervises master- / PhD- students, and give lectures at meetings, conferences and for students at University level. Her major interests are congenital genetic disorders, syndromology, and dysmorphology. She is also interested in benefits and consequences of genetic testing for the families. Her PhD work focused primarily on women's experiences of being carriers for X-linked disorders.

Dr Thomas Werge

Thomas Werge is the director of the Institute for Biological Psychiatry, Copenhagen University Hospital and Professor at the Department of Clinical Medicine, University of Copenhagen. He co-founded the national iPSYCH Initiative, and co-directs the Lundbeck Foundation Center for Geo-Genetics, University of Copenhagen. Werge has been a founder and leader of numerous genomics consortia, and directing the identification of common as well as rare genomic, risk-variants in and across the mental disorders. He has pioneered merging the otherwise distinct disciplines of genomic discovery and population-bases epidemiology to identify and characterize the clinical presentations and characteristics of genetics risk in mental disorders at the population-level. Further, he directed studies documenting that life-span trajectories of comorbidity in mental disorders are highly stable and genetically rooted rather than random co-occurrence of comorbidity, thus informing both genomics investigation as well as healthcare provision re. risk assessment, clinical prediction and decision support. Most recently, Werge has engaged in studies on the evolution of the genomics of human brain disorders throughout the past 10,000 years of modern humans, tracking recently recognized disease variants back in time through analyses of remains of ancient skeletons.

Dr Stefan Winblad

Stefan Winblad is a licensed psychologist, senior lecturer, researcher and associate professor at the Department of Psychology, University of Gothenburg, Sweden. He is affiliated with the Neuromuscular center at the Sahlgrenska University hospital and the research group on Cognitive neuroscience at the Department of psychology in Gothenburg.

Dr Winblad's research is focused on clinical neuropsychology in psychiatric and neurological disorders and the interplay between genes, brain, and behavior during the life span. A specific interest concerns cognitive, emotional, and behavioral dysfunctions in muscular dystrophies, such as Myotonic dystrophy type 1 and Duchenne muscular dystrophy and how dysfunctions develop during life. Dr Winblad is engaged in several ongoing cross-sectional and longitudinal studies on muscular dystrophies, and he collaborates with European research groups on the same topic.

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Educational Day Programme

Time	Educational Day: Thursday 8th September 2022 Venue: Oslo Kongressenter
08:45 – 09:30	**Registration and Coffee**
09:30 – 09:45	Welcome from the Conference Organisers
09:45 – 10:45	**KEYNOTE:** Professor Connie Kasari – Improving Social Communication Outcomes For Young Children With Autism And Other Neurodevelopmental Disorders
10:45 – 11:00	**Morning Refreshments**
11:00 – 11:45	**KEYNOTE:** Dr. Kaja Selmer – The Impact of Epilepsy on Behavioural Phenotypes - and Vice Versa?
11:45 – 12:30	Free Communications (2 x 20 min)
	Jente Verbesselt – Comparison of behavioural and socio-communicative capacities in school-aged children with 16p11.2 deletion and their siblings
	Dr Sissel Berge Helverschou – Bridging the gap between research and clinical practice; Findings from a Nationwide, Multicentre Mental Health Service for adults with Autism and Intellectual disability
12:30 – 13:30	**Lunch**
13:30 – 14:30	**KEYNOTE:** Professor Ann Swillen – The Neurodevelopmental Profile and Stages of Regression in Patients With Phelan Mc-Dermid Syndrome
14:30 – 15:00	**Afternoon Refreshments and Exhibitors**
15:00 – 16:00	Free Communications (2 x 30 min)
	Lauren Shelley – An examination of the caregiver-reported profile and function of behaviour directed towards others (aggressive behaviour) in children and adults with SATB2-associated syndrome
	A/Prof Honey Heussler – An Open-Label, Tolerability and Efficacy Study of ZYN002 (Cannabidiol) Administered as a Transdermal Gel to Children and Adolescents with 22q11.2 Deletion Syndrome (INSPIRE)
19:00 – 20:30	**Welcome Reception** – Oslo Rådhus

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Research Symposium Programme

Time	Day 1, Friday 9th September 2022 Venue: Oslo Kongressenter
08:15 – 08:45	**Registration (for new arrivals) and Poster Set-up**
08:45 – 09:00	Welcome from the Conference Organisers
SESSION 1 – Big Data in the Nordic Countries	
09:00 – 09:45	**KEYNOTE:** Professor Thomas Werge – From Cross-Sectional to Longitudinal Medicine
09:45 – 10:15	**KEYNOTE:** Dr. Ida Elken Sønderby – Using recurrent rare copy number variants carriers to gain insight into human neurodevelopment and disease
10:15 – 10:30	**Morning Refreshments**
10:30 – 11:00	**KEYNOTE:** Dr. Ellen Melbye Langballe – The Norwegian Down Syndrome and Dementia Study
11:00 – 11:45	Free Communications (2 x 20 min)
	Dr Jeanne Wolstencroft – IMAGINE-ID Longitudinal Study: Mental health and behaviour in a National Cohort of UK Children with Intellectual Disability of genetic aetiology
	Dr Sabine Mous – Autism symptom profiles in children and young adults with Fragile X Syndrome, Neurofibromatosis Type 1, Tubereus Sclerosis Complex and Angelman Syndrome
11:45 – 12:30	Free Communications (2 x 20 min
	Professor Randi Hagerman – Features of the Fragile X-associated Tremor/Ataxia (FXTAS) in Premutation Carriers
	Professor Flora Tassone – Somatic CGG instability in female FMR1 premutation carriers: Potential Clinical implications
12:30 – 13:45	**Lunch and Posters**

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Time	**Day 1, Friday 9th September 2022** Venue: Oslo Kongressenter
SESSION 2	
13:45 – 14:30	**Free Communications** (3 x 15 min)
	Dr Ramkumar Aishworiya – Clinical Phenotype and Molecular Biomarkers in Fragile X Syndrome
	Elise Pelgrims – Terminal Triplications of 1p36.3 are Causing a Remarkable Overlapping Facial and Behavioural Phenotype
	Dr Cristan Farmer – An Anchor-Based Approach to Determining Minimal Clinically Meaningful Change in Cognitive and Adaptive Behavior Ability Scores: Indexing Against Key Developmental Milestones
14:30 – 15:00	**KEYNOTE:** Dr. Charlotte von der Lippe – The Why, What, When and How of Genetic Testing
15:00 – 15:45	**Free Communications** (3 x 15 min)
	Professor Donna McDonald-McGinn – Findings in individuals with chromosome 22q11.2 copy number variants diagnosed in adulthood
	Dr. Nicole Tartaglia – The eXtraordinarY Babies Study: Developmental Profiles of Infants with Prenatally Identified Sex Chromosome Trisomies
	Dr Shuting Zheng – Bias in measurement of autism symptoms by language level and nonverbal mental age in minimally verbal children with neurodevelopmental disorders
15:45 – 16:15	**Afternoon Refreshments and Posters**
SESSION 3	
16:15 – 17:15	**THE TOM OPPÉ DISTINGUISHED LECTURE :** Professor Kevin Mitchell – What Have We Learned From Psychiatric Genetics?
19:30	**Conference Gala Dinner – Oslo Kongressenter**

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Day 2, Saturday 10th September 2022 Venue: Oslo Kongressenter	
SESSION 4	
09:00 – 09:45	**KEYNOTE:** Professor David Skuse – Gene Functional Impairment and Its Correlation with the Phenotypic Profile of ASD in a National Cohort of UK Children with Intellectual Disability
09:45 – 10:15	**KEYNOTE:** A/Prof. Johan Lundin Kleberg – Reinforcement Learning and Social Attention in Rare Genetic Disorders: Results from the Swedish UNIKA Study
10:15 – 10:45	**Morning Refreshments**
SESSION 5	
10:45 – 11:30	**KEYNOTE:** Dr. Stefan Winblad – Neurocognition And Behaviour in Muscular Dystrophies
11:30 – 12:15	**KEYNOTE:** Professor Pat Howlin – Changes in mental health, quality of life and social inclusion in older autistic adults
12:15 – 13:15	**Lunch**
SESSION 6	
13:15 – 13:40	**THE PAT HOWLIN AND LECLEZIO-DE VRIES PRIZE LECTURE:** Dr. Stacey Bissell, on behalf of the TAND Consortium – The TAND Toolkit App – Participatory Development of a Mobile App to Reduce the TSC-Associated Neuropsychiatric Disorders (TAND) Identification and Treatment Gap
13:40 – 14:00	Free Communication (1 x 20 min)
	Dr Kate Woodcock – Collaborating with the Global PWS Community to Better Understand Support and Advocacy Needs
14:00 – 14:15	A Presentation about SSBP 2023
14:15 – 14:30	**Afternoon Refreshments**
14:30 – 15:20	SSBP AGM and Award Ceremony
15:20 – 15:50	Panel Discussion
	Prof. Petrus de Vries (chair) – Usefulness of an Autism / ASD Diagnosis in Rare Genetic Disorders with ID
15:50 – 16:00	**Closure of Research Symposium**

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1. KEYNOTE: Improving Social Communication Outcomes for Young Children with Autism and Other Neurodevelopmental Disorders

Kasari, C.
University of California, Los Angeles

The ability to engage with others and to communicate are primary targets of early interventions for children with autism. This talk will discuss what we have learned from over twenty years of research on interventions for social communication outcomes for young children with autism, and more recent expansion to children with other neurodevelopmental disorders. A focus will be on children who are often not included in research studies, including those who are traditionally marginalized and minoritized, who are non-speaking, and who are intellectually disabled. New research approaches to personalizing interventions for all children will be addressed, emphasizing what research can contribute to clinical practice.

Keywords: Early intervention, autism, adaptive designs, joint attention, language

2. KEYNOTE: The Impact of Epilepsy on Behavioural Phenotypes – and Vice Versa?

Selmer, K.

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Epilepsy is a heterogeneous group of disorders, characterized by disturbance of neuronal signalling causing recurrent epileptic seizures. A high prevalence of neuropsychiatric disorders and behavioural phenotypes has been acknowledged for decades, however, how seizures and the behavioural phenotypes interact remains elusive. Location of epileptic focus, the affected neuronal networks, and shared genetic predisposition are all possible mechanisms of interaction, which may play a role in the final outcome. One type of epilepsy where behavioural phenotypes are particularly prevalent and extensively studied is juvenile myoclonic epilepsy (JME), the most common epilepsy in adolescents. As such, JME presents a model for investigating the interactions of seizures and behavioural disorders, offering a gateway to improved understanding and better management of both.

3: Comparison of Behavioural and Socio-Communicative Capacities in School-Aged Children with 16p11.2 Deletion and Their Siblings

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

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

Background: 16p11.2 deletion syndrome (16p11.2 DS) is a recurrent copy number variant (CNV) that occurs de novo in approximately 70% of cases and confers risk for neurodevelopmental difficulties such as cognitive, behavioural and speech-language problems. The purpose of the current study is to further delineate and compare the behavioural and socio-communicative phenotype of school-aged children with 16p11.2 DS and their non-carrier siblings.

Methods: Behavioural and socio-communicative capacities were assessed by means of three standardized questionnaires completed by parents: Child Behaviour Checklist 6-18 (CBCL), Children's Communication Checklist (CCC-2-NL) and Social Responsiveness Scales (SRS-2-NL). The CBCL evaluates emotional and behavioural problems, whereas the SRS-2 screens deficits in social behaviour associated with autism spectrum disorders (ASD). The CCC-2 assesses everyday communicative situations including speech-language and social abilities. Questionnaires of 24 children with 16p11.2 DS between 6-16 years old were analysed and compared to those of their siblings (n=12). Scores of both groups were also compared to normgroup scores.

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

Conclusions: In this study, school-aged children with 16p11.2 DS show high rates of socio-communicative, social responsiveness and behavioural problems compared to their siblings and the typical population, which is in line with the literature. These findings point to the high prevalence of autistic traits and diagnoses in this CNV population. Moreover, patients with both socio-communicative and behavioural problems are vulnerable and need closer clinical follow-up and care.

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

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4: Bridging The Gap Between Research and Clinical Practice; Findings from a Nationwide, Multicentre Mental Health Service for Adults with Autism and Intellectual Disability

***Helverschou S.B.*[1]**

[1] *NevSom, Norwegian Centre of Expertise for Neurodevelopmental Disorders and Hypersomnias, Oslo University Hospital*

Background: The identification and treatment of psychiatric disorders in individuals with autism presents many challenges. Strategies to improve the quality of mental health services for autistic adults with ID are needed.

Methods:

Aim: explore the outcome, in terms of patient change, of a professional network and a standardised protocol for clinical assessment as an implementation strategy to improve services and outcome for these patients.

Eight clinical centres participated in a specialised professional network. Implementation of research-based strategies in clinical practice and professional competence development was emphasized. Referred patients were assessed three times, at referral (T1), after one year (T2) and after two years (T3) by a standardised assessment protocol. Changes in psychiatric symptoms and behaviour problems over time were assessed with Psychopathology in Autism Checklist (PAC) and Aberrant Behavior Checklist (ABC).

Results: 132 patients age 16 – 66 years (43 females, 89 men), 87 mild / moderate ID and 45 severe / profound ID, participated. All had been clinically diagnosed with ASD + ID.

Patients showed significant ($p \geq .001$) reduction in psychiatric symptoms from T1 to T2 on the psychosis, depression and anxiety subscales of the PAC, but not significant reduction on the obsessive compulsive disorder subscale. The improvements were maintained from T2 to T3. Patients showed significant ($p \geq .001$ or < 0.01) improvements on the ABC total score and on all ABC subscales, except inappropriate speech, from T1 to T2, and the improvements were maintained from T2 to T3.

Conclusions: The combination of a professional network and a standardised protocol for clinical assessment has promise as a strategy for improving professional competence and facilitating specialised mental health services for autistic individuals with ID and psychiatric disorders across an extensive geographical area.

Keywords: Autism, psychiatric disorders, treatment, clinical services

5. KEYNOTE: The Neurodevelopmental Profile and Stages of Regression In Patients with Phelan Mc-Dermid Syndrome

Swillen A.A.E.[1,2]*, Dille Y.I.*[3]*, Lagae L.*[4]*, Sevenants L.*[5]*, Wouters C.*[1]*, Vogels A.*[1]*, Van Buggenhout G.*[1]

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Introduction: Phelan-McDermid syndrome (PMS) is characterized by a variety of clinical symptoms with heterogeneous degrees of severity, including intellectual disability (ID), absent or delayed speech, and autism spectrum disorders (ASD). It results from a deletion of the distal part of chromosome 22q13 that in most cases includes the SHANK3 gene. SHANK3 is considered a major gene for PMS, but the factors that modulate the severity of the syndrome remain largely unknown.

Aim: To characterize the neurodevelopmental profile in Phelan Mc-Dermid Syndrome (PMS) and describe the nature and trajectory of regression.

Methods: The clinical and developmental data of 24 patients (13 males (54.2%)/11 females (46.8%); mean age 25 years 6 months, range 6-56y) with a confirmed 22q13.3 terminal deletion followed at the Centre for Human Genetics, University Hospital Leuven were evaluated. All patients were seen by at least 2 specialists of the multidisciplinary PMS team (clinical geneticist, clinical-educational psychologist, child neurologist, child psychiatrist). The neurodevelopmental profile was examined using a mixed methods approach combining both cross-sectional and longitudinal data. Development, communication and behaviour was assessed by standardized instruments such as Bayley Mental Scales of Development- third version (BSID-III NI), the Adaptive Behaviour Scales, third version (ABAS-III NI) and child psychiatric clinical expert evaluation.

Results: All patients had a moderate to severe intellectual disability (ID). Significant loss of skills was present in 19/24 or 79% of subjects. The first manifestations of regression occurred, on average, at the age of 7y 6mo (age range 5 -11y). Active vocabulary was primarily affected followed by, in order of loss, psychosocial adaptability, fine motor skills and walking ability. The course of regression was characterized by a recognizable four-stage pattern: in the first stage a pronounced and abrupt decline of active vocabulary was observed. In the second stage, a (prolonged) period of stagnation of regression was seen. The third stage was characterized by acute neuropsychiatric decline (e.g., catatonia, hallucinations, psychosis). Acute events such as severe sickness, hormonal shifts, and psychosocial stress frequently preceded the fourth and final stage, characterized by severe neuro-motor regression.

Conclusion: Neurodevelopmental regression across age is a key feature of PMS. A four-stage neurodevelopmental regression is observed in many patients which is important to take into account for clinical follow-up and changing needs of support.

Keywords: Phelan Mc Dermid, 22q13.3 deletion syndrome, neurodevelopment, regression

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6: An Examination of the Caregiver-Reported Profile and Function of Behaviour Directed Towards Others (Aggressive Behaviour) in Children and Adults with SATB2-Associated Syndrome

***Shelley L.*[1], *Tarver J.*[1], *Crawford H.*[2], *Richards C.*[3], *Waite J.*[1]**

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[2] *Warwick Medical School, University of Warwick, UK*

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Background: SATB2-associated syndrome (SAS) is characterised by intellectual disability, severe speech delay, and palatal and dental problems. An estimated prevalence of 77% is reported for aggressive behaviour. However, no research has investigated the profile and functions for aggressive behaviour in SAS.

Methods: Stage 1: Thirty-seven caregivers of individuals with SAS (M_{age} 11.28 years; range 3-33 years) completed questionnaire measures of adaptive ability, aggressive behaviour, and behavioural function. Functions of aggressive behaviour in SAS were compared to data available for functions of aggressive behaviour in individuals with Lowe syndrome (LS; M_{age} 17.15 years; range 6-34 years). Stage 2: Thirty-four in-depth semi-structured interviews were conducted to further understand setting events, motivating operations, and consequences of aggressive behaviour in SAS.

Results: Stage 1: 86.5% of the SAS group engaged in aggressive behaviour during the past month. Frequently reported topographies were pull/grab (87.5%) and hit with body part (68.8%) or object (53.1%). Functions frequently meeting clinical cut-off were tangible (43.8%), routine/repetitive behaviour (37.5%), demand escape (31.3%) and pain/discomfort (31.3%). There were differences in the proportion of individuals meeting cut-off across functions (Q(7)=38.15, p=<.001). Aggression severity positively correlated with the number of functions meeting cut-off ($\boldsymbol{r}_s$=.395, p=.026). Self-help and language ability negatively correlated with indicators of aggression severity ($\boldsymbol{r}_s$=-.386, p=.029 and $\boldsymbol{r}_s$=-.457, p=.009). Cross-syndrome comparisons revealed differences in the proportion of individuals meeting cut-off for tangible, which approached significance ($\chi^2(1)=3.59$, p=.058), no further differences were found. Stage 2: The interviews identified factors which may underpin functions serving aggressive behaviour in SAS.

Conclusions: This study supports the utility of combining questionnaire and interview methodology to profile behaviour. Findings indicate similarities in functions for aggressive behaviour in SAS and LS; however, similar presentations of behaviour and function may be underpinned by differing phenotypic pathways. Understanding pathways to aggressive behaviour has clinical implications for implementing tailored behavioural interventions.

Keywords: Behaviour that challenges, aggressive behaviour, function, SATB2-associated syndrome, SATB2, Lowe syndrome

7: An Open-Label, Tolerability and Efficacy Study of ZYN002 (Cannabidiol) Administered as a Transdermal Gel to Children and Adolescents With 22q11.2 Deletion Syndrome (INSPIRE)

Heussler H.[1], Cohen J.[2], Buchanan C.[3], O'Neill C.[4], Sebree T.[4], O'Quinn S.[4]

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[2] *Genetic Clinics Australia, North Caulfield, Victoria, AU*

[3] *Greenwood Genetic Center, Greenville, SC, USA*

[4] *Zynerba Pharmaceuticals, Devon, PA, USA*

Background: ZYN002 is a pharmaceutically produced transdermal cannabidiol gel in development for the behavioural symptoms in 22q11.2 Deletion Syndrome (22q), Fragile X syndrome and autism spectrum disorder. INSPIRE is an open-label, phase 2 trial to evaluate the safety/tolerability and efficacy of ZYN002, in children and adolescents ages 4 to < 18 years, in the treatment of 22q.

Methods: Males and females with 22q confirmed by genetic testing, with or without autistic features, a Clinical Global Impression-Severity (CGI-S) score ≥ 4 and a Paediatric Anxiety Rating Score-Revised (PARS-R) score ≥ 10 were enrolled. Patients weighing ≤ 35 kg received 250 mg/day and those weighing > 35 kg received 500 mg/day of ZYN002 in divided doses every 12 hours added to current stable therapy. Patients with < 25% improvement from baseline in the Aberrant Behaviour Checklist-Community (ABC-C) irritability subscale at week 6 could have their dose increased to either 500 mg/day or 750 mg/day based upon weight. Patients with ≥ 35% improvement on the ABC-C irritability subscale at week 14 (end of Period 1) could continue into Period 2 for an additional 24 weeks. Safety assessments included adverse events, vital signs, laboratories, and electrocardiograms. Efficacy assessments included change from baseline on the ABC-C, PARS-R, CGI-Improvement (CGI-I), Anxiety, Depression and Mood Scale (ADAMS) and the Children's Sleep Habits Questionnaire (CSHQ). A qualitative caregiver reported behavioural problems survey was also collected.

Results: 20 patients, 60% males, with a mean age of 9.9 years (5 to 15 years) were enrolled. As of 20-May-2022, 14 patients completed and 2 withdrew from Period 1; 9/14 patients had ≥ 35% improvement on the ABC-C irritability subscale and entered Period 2. No serious adverse events had been reported.

Conclusions: Safety and efficacy data for Period 1 will be reported, including impact on behavioural symptoms and outcomes related to anxiety.

Keywords: 22q.11.2, deletion syndrome, cannabidiol, irritability, anxiety

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8. KEYNOTE: From Cross-Sectional to Longitudinal Medicine

Werge, T.

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LF Center for Geogenetics, Globe Institute, University of Copenhagen

Although Western medicine may trace its root to the ancient Greek cultures, it traditionally takes a cross-sectional approach the disease, being mainly concerned with manifest disease or prodromal expressions thereof, while paying less attention to the longitudinal notion of the healthy-life expectancy.

This approach to health and disease not only has barring on the ability of the healthcare system to target adequate screening and prevention strategies to the need of the individual, but it also has implications for our concept and understanding of the nature of disease.

In fact, comorbidity, while a well-known and important concept in medicine and healthcare provision, is poorly explored across the diagnostic spectra and between organ systems. Little if anything is known of the segregation patterns across generations, and thus the heritability, of complex disease presentation, which hampers scientific advancement and the realization of precision medicine

We have used nationwide demographic registers to reconstruct and crosslink the genealogy of individuals living in Denmark with population-complete healthcare records to show that illnesses, both within or and across organ systems, are causally highly related; including diseases that occur at different time points throughout life.

To explore the nature that such complex, temporal presentations of multiple disorders, we built disease trajectories for individuals in the Danish population diagnosed with schizophrenia. We considering all other mental disorders as independent comorbid events in the lives of these individuals, and examined structures, stability and causes of the resulting disease trajectories and showed them to be highly stable, predictable, as well as reliant on shared causal factors.

Keywords: Disease trajectories, Co-heritability, Precision health, Genealogy, Epidemiology, Psychiatry

9. KEYNOTE: Using Recurrent Rare Copy Number Variants Carriers to Gain Insight into Human Neurodevelopment and Disease

Sønderby I.E.[1,2,3]*, Bakken N.R.*[2]*, Birkenæs V.*[2]*, Athanasiu L.*[2]*, Djurovic S.*[2,3]*, Nærland T.*[3]*, Andreassen O.A.*[2,3]

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[2] *Norwegian Centre for Mental Disorders, University of Oslo, Norway*

[3] *K. G. Jebsen centre for neurodevelopmental disorders, Oslo, Norway*

Carriers of certain copy number variants (CNVs), i.e. regions of the genome either deleted or duplicated, are at elevated risk for a wide range of medical and behavioural consequences including brain disorders such as autism, schizophrenia and intellectual disability.

Research both on both rare and common genetic variants suggests that brain disorders are highly interlinked. For instance, reciprocal CNVs at one genomic loci (deletions and duplications at each end of the dosage response) may be associated with the same disorder. On the other hand, one specific CNV may confer elevated risk for several different (brain) disorders. Thus, CNV studies may help us disentangle the mechanisms behind interrelated disorders and their influence on disease outcome (both mental and somatic).

Ida will discuss work on CNVs with emphasis on large population datasets. She will touch upon how recurrent CNVs affect brain structure providing examples from the Enhancing Imaging Genetics through Meta-Analysis (ENIGMA)-CNV working group. Likewise, she will present her recent work on CNV carriers from the Norwegian mother, father and child study (MoBa) - a Norwegian pregnancy cohort with 114k children and their parents.

Keywords: Copynumbervariants, neurodevelopmental

10. KEYNOTE: The Norwegian Down Syndrome and Dementia Study

Langballe, E.M.
Norwegian National Centre for Ageing and Health

Down syndrome (DS) is caused by having a third copy of chromosome 21 (trisomy 21) and is the most common genetic condition associated with intellectual disability. DS involves an excessive lifetime risk of Alzheimer's disease (AD) estimated to 90%. AD is now the leading cause of death in the DS population. Although international progress has recently been made in increasing the standard of the clinical AD diagnostic work-up for people with DS, common assessment procedures and tools, including biomarkers and the measurement of cognitive, adaptive, behavioural and psychological symptoms, have not yet been investigated or implemented in the habilitation units at the specialist health services in Norway. For these reasons, the Norwegian National Centre for Ageing and Health have initiated the Norwegian Down Syndrome and Dementia Study. The overarching aims are to evaluate the psychometric properties of diagnostic tools for individuals with DS and investigate the association with non-invasive plasma biomarkers of AD to improve clinical practice and to inform future clinical trials. The data collection is ongoing as of June 2022. The Norwegian Down syndrome and dementia study will be presented at the conference.

Keywords: Down Syndrome, Dementia, Alzheimer's Diseases, Ageing, Study Design

11: IMAGINE-ID Longitudinal Study: Mental Health and Behaviour in a National Cohort of UK Children with Intellectual Disability of Genetic Aetiology

Wolstencroft J.[1]*, Housby H.*[1]*, IMAGINE ID Consortium*[1]*, Skuse D.*[1]

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Background: IMAGINE is a national longitudinal study of behavioural problems and psychiatric risk in children with intellectual disability (ID) of known genetic origin. Our main aim is to compare the trajectory of development of mental health and behavioural difficulties experienced by participants, and the impact on their families, to data from UK national studies of typical children collected by identical instruments over the same time period.

Methods: IMAGINE participants (6-16 years) were initially recruited from UK NHS Genetic Services between 2015-2020. Caregivers. (n=804) completed the SDQ in 2015-9 (T1) and again in 2021 (T2). Age-matched typical comparisons (2,602) completed SDQs in 2017 (T1) and 2021 (T2). SDQ Total Difficulties change scores were calculated in both samples, and algorithmically defined as indicating significant deterioration, no change or improvement.

Results: IMAGINE participants had significantly higher rates of mental health and behavioural difficulties than comparison children at both T1 and T2 but, proportionately more of the IMAGINE cohort improved (35.4% vs 21.8%) and fewer deteriorated (24.4% vs 39.2%) than in the national cohort (p<.0001).

Conclusions: IMAGINE participants are more likely to have clinically significant mental health and behavioural difficulties than neurotypical children at all ages, but a follow-up into middle childhood and adolescence indicates a trend to improvement in children with ID of genetic aetiology, and greater deterioration in neurotypical comparisons. Covid-19 may have differentially impacted the mental health outcomes of IMAGINE and typical children over this period.

Keywords: Intellectual disability, mental health, behaviour, genetics, Covid.

12: Autism Symptom Profiles in Children and Young Adults with Fragile X Syndrome, Neurofibromatosis Type 1, Tuberous Sclerosis Complex and Angelman Syndrome

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[2] *ENCORE expertise center, Erasmus MC Sophia Children's Hospital, Rotterdam, the Netherlands*

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

Methods: Data on ASD symptomatology (Autism Diagnostic Observation Scale (ADOS-2) & Social Responsiveness Scale (SRS-2)) was collected in patients with FXS (n=43), AS (n=45), TSC (n=83) and NF1 (n=238). To identify groups of individuals with similar ASD profiles, latent profile analyses were performed. Clinical characteristics for the latent profiles were compared and auxiliary analyses were performed to determine the probability of each patient group belonging to each latent profile.

Results: A four-profile model was identified as best fit for the ADOS, with a (1)'Overall low ASD symptom profile', (2)'Elevated Social Affect, low Restricted/Repetitive Behaviors symptom profile', (3)'Low Social Affect, elevated Restricted/Repetitive Behaviors symptom profile' and (4)'Overall elevated ASD symptom profile'. For the SRS a three-profile model was found, with a (1)'Low ASD symptom profile', (2)'Elevated ASD symptom profile' and (3)'High ASD symptom profile'. Differences were observed in sex and IQ between profiles. All patient groups were represented in each profile, but there were large differences in the distribution of patient groups over profiles.

Conclusions: A large variability in ASD symptoms between and within FXS, AS, TSC and NF1 was found, and multiple distinct symptom profiles exist. Factors like sex and IQ potentially play an important role in this distinction. This study endorses the importance of and need for a personalized approach in the identification and treatment of ASD difficulties in rare genetic syndromes.

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

13: Features of The Fragile X-Associated Tremor/Ataxia (FXTAS) in Premutation Carriers

Hagerman R.J.[1,2]*, Santos E.*[1]*, Johnson D.*[1]*, Kim K.*[1]*, Tassone F.*[1,3]

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[2] *UC Davis Pediatrics Department, USA*

[3] *Department of Biochemistry and Molecular Medicine, UC Davis, USA*

Background: Females have a lower incidence of FXTAS and lower severity compared to males but phenotypic differences exist.

Methods: 108 premutation carriers with FXTAS including 65 males and 43 females underwent a detailed evaluation involving neuropsychiatric testing, MRI imaging, biomarker studies and a neurological evaluation.

Results: Intention tremor was the most common neurological symptom (68.5%) followed by postural tremor (51.9%) and head tremor (25%). Parkinsonian features were significantly higher in males (36.9%) compared to 13.95% in females (p=0.009). In patients with Parkinsonian features, 41.4% had FXTAS stage 4 or above, compared to 18.4% of those without Parkinsonian features (p=0.047). Correlation analyses between clinical onset of tremor and molecular measures revealed significant negative correlations between CGG repeat allele size and the age of onset of both tremor (ρ = -0.204, p=0.048) and ataxia (ρ = -0.274, p=0.022). In men, increasing CGG repeat allele size correlated with higher FXTAS staging (p=0.046) and lower cognitive function (p=0.0351). However, women experience significantly more pain symptoms than men, particularly allodynia (20% vs. 2.0%, p=0.008), peripheral neuropathy pain (43.9% vs. 25.4%, p=0.0488), migraines (43.9% vs. 14.5%, p=0.0008), fibromyalgia (26.8% vs. 0%, p=0.0071) and back pain (48.5% vs. 23.4%, p=0.008). Onset of peripheral neuropathy predicts the onset of ataxia (β=0.63±0.25, p=0.019) and tremor (β= 0.56±0.17, p=0.004) across gender. Women also report significantly more anxiety (82.9% vs. 39.7%, p<0.001) than men. Females with FXTAS are significantly more likely to be taking any pain medication (58.54% females vs. 36.51% males, p=0.0271).

Conclusions: There are significant differences between males and females with FXTAS and both diagnostic and treatment endeavours may differ. Psychiatric and pain symptoms are more common in females with FXTAS and these problems should be treated early. The higher CGG repeat numbers puts individuals at greater risk to develop FXTAS early.

Keywords: Premutation, FMR1, FXTAS, Tremor, Ataxia, neuropsychiatric features

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14: Somatic CGG Instability in Female FMR1 Premutation Carriers: Potential Clinical Implications

*Aishworiya R.[1,2], Hwang Y.[3], Durbin-Johnson B.[4], Hagerman R.[1,5], **Tassone F.**[1, 3]*

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Background: Premutation (PM) carriers of the FMR1 gene are at higher risk to develop PM associated disorders including Fragile X-associated Tremor/Ataxia Syndrome (FXTAS), Fragile X-associated Primary Ovarian Insufficiency (FXPOI), and Fragile X-Associated Neuropsychiatric Disorders (FXAND). We have recently reported somatic CGG allele instability in female PM carriers; however, its clinical significance remains unclear. The aim of this study was to examine the potential clinical association between somatic instability and PM associated disorders.

Methods: Participants comprised of 425 female PM carriers aged 0 – 90 years. FMR1 molecular measures were carried out for all subjects. Clinical information on the presence *of FXTAS, FXPOI, FXAND disorders including autism spectrum disorder, ADHD, chronic medical and auto-immune conditions, were obtained from medical record review. Statistical analysis utilized Spearman's correlation tests and Wilcoxon rank-sum tests to test for degree of somatic instability and presence of various clinical conditions. Participants were divided in sub-groups (aged ≥25, N=378 and aged ≥50, N=134) for analysis related to the presence of FXPOI and FXTAS respectively.*

Results: In the overall sample (N=425), degree of instability was significantly higher in subjects with a diagnosis of ADHD (median difference 2.5 vs 2.0, $p = 0.026$) compared to those without, and, lower in subjects with a SCID diagnosis (0.0 vs 2.5, $p = 0.0428$) in the sub-group with FXTAS. *FMR1 mRNA* expression was significantly higher in subjects with psychiatric disorder diagnosis ($p = 0.0017$); specifically, in those with ADHD ($p= 0.009$), and with depression ($p = 0.025$).

Conclusions: Somatic *FMR1* allele instability was associated with the presence of ADHD in female PM carriers and *FMR1* mRNA levels were associated with the presence of mental health disorders. Our findings suggest a potential role of instability in the clinical phenotype of PM carriers and may potentially guide clinical prognostication and management.

Keywords: Fragile X premutation, somatic instability, ADHD

15: Clinical Phenotype and Molecular Biomarkers in Fragile X Syndrome

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Background: Greater understanding of how molecular biomarkers in Fragile X Syndrome (FXS) associate with clinical features can guide prognostication and management of individuals with FXS. This study's aim was to examine molecular markers of FXS in relation to the clinical phenotype.

Methods: Baseline data of 52 participants with FXS ages 6-40 years enrolled in a metformin clinical trial were utilized: Leiter-III, Vineland Adaptive Behavior Scales (VABS-III), Expressive Language Scale (ELS), NIH Toolbox, Autism Diagnostic Observation Schedule-2 (ADOS-2), the Pediatric Quality of Life (PedsQL), Anxiety, Depression and Mood Symptoms questionnaire (ADAMS), Aberrant Behavior Checklist (ABC-CFX), Child Sleep Habits Questionnaire (CSHQ), and Swanson, Nolan, and Pelham-IV (SNAP-IV) Questionnaire. Molecular biomarkers from blood sample included *FMR1* mRNA, MMP 9 and CYFIP. Tests of correlation (Spearman's correlation) were used with significance set at p-value <0.05.

Results: The mean non-verbal IQ score was 46.3 (SD 13.5) and VABS adaptive behaviour composite (ABC) score was 49.1 (16.1). Levels of *FMR1* mRNA were positively correlated with the VABS (rs = 0.35, p=0.02), ELS composite score (rs = 0.45, p=0.01) and several Toolbox measures; and negatively correlated with the SNAP-IV combined score for ADHD (rs = -0.30, p=0.04). MMP9 was correlated positively with weight (rs = 0.67, p<0.001) and negatively with the non-verbal IQ score (rs = -0.42, p=0.002), VABS ABC score (rs = -0.34, p=0.02), and the SNAP-IV combined score (rs = -0.48, p<0.001). CYFIP was positively correlated with the total comparison score on the ADOS (rs = 0.44, p=0.006).

Conclusions: Surprising and new findings included positive correlation of MMP9 with weight and CYFIP with ADOS-2. The mRNA positive correlations with VABS, ELS and Toolbox measures reflect the importance for cognitive, adaptive and language functions for those with mosaicism who may have more mRNA and hence producing FMRP. These biomarkers will be utilized for treatment effects with our metformin-controlled trial.

Keywords: Fragile X syndrome, CYFIP, FMR1 mRNA, Cognition, Behaviour

16: Terminal Triplications of 1p36.3 are Causing a Remarkable Overlapping Facial and Behavioural Phenotype

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Background: Triplications of chromosomal region 1p36.3 are rare. Only one patient has been described, featuring feedings difficulties, developmental delay (DD) across all developmental domains, facial dysmorphic features, seizures, and severe intellectual disability (ID). Here we report three additional patients, including two patients from Decipher (4077, 259927).

Methods: Partially overlapping *de novo*, triplications of 1p36.3 were identified by chromosomal microarray analysis in patient 1 (hg19:1p36.3(723,318-2,332,089)x4), patient 2 (hg19:1p36.3(1823921-5384328)x4) and patient 3 (hg19:1p36.3(759760-3161082)x4). In addition, patient 3 has a 1Mb terminal deletion on 12q (hg19:1 2q24.33(132806913-133767986)x4), not comprising known genes for autosomal dominant disorders.

Results: Patient 1 is a 14-year-old girl presenting moderate ID and dysmorphic facial features, including ptosis, epicanthic folds, hypertelorism, arched eyebrows, upturned nares, low set ears, and little facial expression. Pregnancy was complicated by intrauterine growth retardation. During infancy she had severe feeding problems and failure to thrive, requiring gastrostomy feeding. She had AV-block grade I, and she was treated for myoclonic epilepsy. Cognitive testing measured by the WPSSI-III-NL at age 5, showed a mild to moderate ID with a full scale IQ of 67, with a disharmonic profile (Verbal IQ 82; Performance IQ 67). She was diagnosed with Attention Deficit Disorder, Autism Spectrum Disorder and Developmental Coordination Disorder. At age 14, she has pronounced fears as well as sensory integration problems, measured with the SP-NL. Patient 2 is a 30-year-old female with mild ID, feeding difficulties during infancy, and a striking similar facial phenotype (ptosis, epicanthic folds, arched eyebrows, malar flattening and upturned nares). She has autistiform symptoms as well. Patient 3 is a 14-year-old boy with mild DD and facial features, reminiscent of trisomy 21, including upslanting palpebral fissures and ptosis.

Conclusion: We show that terminal triplications of 1p36.3 constitute a novel clinical recognizable chromosomal syndrome with intellectual disability, behavioural issues, and a typical facial gestalt.

Keywords: CNV – triplication – 1p36.3 – developmental delay

17: An Anchor-Based Approach to Determining Minimal Clinically Meaningful Change in Cognitive and Adaptive Behaviour Ability Scores: Indexing Against Key Developmental Milestones

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Background: For rare genetic conditions associated with neurodevelopmental disorder (GCAND), developmental concepts are attractive treatment targets, but the norm-referenced scores commonly used for the assessment of these concepts have unfavourable properties such as floor effects and poor reliability. The person ability score confers greater power to detect a treatment effect when used in place of the norm-referenced score, but its unitless scale makes the determination of clinically meaningful change difficult.

Methods: We propose that the change in probability of achieving developmental milestones will be a useful anchor for interpreting change in ability score. Here, we lay the theoretical foundation for our efforts to classify clinically meaningful change in person ability scores on developmental measures. We focus on two measures which offer person ability scores and are otherwise feasible outcome assessments for GCAND clinical trials, the Vineland Adaptive Behavior Scales, 3rd Edition and the Bayley Scales of Infant Development, 4th Edition.

Results: The first stage of this project was to convene a panel of experts in child development to identify candidate Vineland and Bayley items. The second stage was to evaluate the reliability and validity of these items for measuring milestone attainment, using data from GCAND natural history studies. Finally, we will exploit the quantitative relationship between the person ability score and the probability of passing an item to derive thresholds for clinical importance of change ability scores.

Conclusions: Observational and empirical data suggest that person ability scores may have better power and responsiveness than norm-referenced scores when used as endpoints in clinical trials for rare genetic conditions. However, establishing the clinical meaningfulness of any endpoint must be a multiprong effort that includes both quantitative and qualitative work. The next stage of this work will be to work with parents, caregivers, and professionals to establish the qualitative evidence for these thresholds.

Keywords: Meaningful change, clinical trials, ability score, adaptive behaviour, cognitive ability

18. KEYNOTE: The Why, What, When, and How of Genetic Testing

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Genetic testing is a standard component of the diagnostic work-up in individuals with significant developmental delay (DD) / intellectual disability (ID). Which specific tests to consider offering is influenced by factors such as family history and clinical phenotype.

Laboratory methods are improving rapidly, as is identification of new associations between DD/ID and specific genes. Access to scientific publications via the internet, mainstream media reports and diagnosis-specific lay groups contribute to the broad availability of knowledge about genetic testing. Parents of children who have DD/ID seek answers to many questions: What caused my child's condition? Is it treatable/curable? What is the prognosis? What follow-up/screening is appropriate? What can we do as parents to help our child develop and thrive? What is the probability of recurrence in a sib? Where can we find reliable information? Can we meet other families in the same situation? Can we participate in research?

Parents are generally positive to genetic testing in the context of DD/ID. A molecular genetic diagnosis is a good starting point for addressing their concerns. However, parents' preconceptions, hopes and expectations relating to genetic testing may be unrealistic. Healthcare professionals should be ready to discuss the limitations as well as the potential benefits of genetic testing in order to facilitate the parents' ability to make an informed choice.

19: Findings in Individuals with Chromosome 22q11.2 Copy Number Variants Diagnosed in Adulthood

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Background: Past medical history and outcomes in adults with 22q11.2 deletion syndrome (22q11.2DS) are relatively limited compared with paediatric reports, as 22q11.2DS is frequently diagnosed in children with congenital heart disease (CHD). In fact, many adults without CHD or psychiatric illness only come to attention following the diagnosis in a child with 22q11.2DS, often born with CHD. Thus, childless individuals may remain undetected until later in life or remain undiagnosed. This may reflect the disconnect between birth prevalence (1/2148) and the relative paucity of adult patients seen even in magnet centres. Here we report findings in 74 individuals diagnosed in adulthood.

Methods: Patient registry and electronic medical records for patients identified via the 22q and You Center at the Children's Hospital of Philadelphia (CHOP) under an IRB approved protocol, were reviewed retrospectively for 837 adult patients a with standard or atypical deletion and 56 of their underage relatives. Exclusions included: 481 patients diagnosed before 18 years; 243 where age at 22q11.2DS diagnosis was not readily available; and 39 who were deceased in childhood. Abstracted data included: demographics, proband status, phenotypic features, educational achievement, employment, relationship/marital status, living situation, and parenting outcomes. The cohort was divided into probands and non-probands for comparative purposes.

Results: Data on 74 patients (21 adult probands and 53 non-probands) diagnosed with a standard or atypical 22q11.2 deletion after 18 years of age were analysed. Atypical deletion size correlated with likelihood of diagnosis as an adult non-proband. Non-proband status was also associated with better educational outcomes and a greater probability of marriage, independent living, and becoming a parent. Employment outcomes and sectors were similar for both probands and non-probands. Few significant differences in phenotypic features were observed between the two groups. Of note, many adults had congenital anomalies associated with 22q11.2DS which could have brought them to attention in childhood.

Conclusions: Our 74 adult patients turned 18 years of age between 1961 and 2016, were diagnosed between 1994 and 2021, and are currently 23 to 78 years old (Mean 42.08). Histories included classically associated features prior to the diagnosis. Men more frequently married (p=0.16). There was no association with likelihood to have a single child or multiple children (p=0.71 and 0.59). Outcomes in adult life, including educational achievement, relationships, and child-rearing will be discussed. In addition, we will present a comparison with outcomes for patients diagnosed before 18 years of age but who are now adults and to those with 22q11.2DupS.

Keywords: 22q11.2, adults, chromosome, outcomes

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20: The Extraordinary Babies Study: Developmental Profiles of Infants with Prenatally Identified Sex Chromosome Trisomies

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Background: Children with sex chromosome trisomies (SCTs: XXY, XYY, XXX) are at risk for cognitive, language, and motor deficits. Broadened use of non-invasive prenatal genetic testing has increased prenatal identification of SCT and provides opportunity to describe and compare health, development, and hormonal trajectories from birth, and to examine predictors of outcomes.

Methods: The eXtraordinarY Babies study includes infants prenatally diagnosed with SCT (n=263; 181 XXY; 26 XYY; 55 XXX) seen at 2, 6, and 12 months and then yearly. For this analysis, one sample t-tests compared scaled scores on the Bayley-3 Scales of Infant Development to the population mean, paired samples t-tests compared expressive vs. receptive language and fine vs. gross motor, and ANOVAs explored scores between SCT subgroups and over time.

Results: There were no differences between SCT subtypes on any of the scales across visits, thus groups were pooled for further analyses. There were no differences in cognitive skills compared to the population mean at all timepoints (Cognitive scale means (SD): 6m 10.2(2.2); 12m 10.3(1.8); 24m 9.7(2.5); 36m 10.3(1.95), p 0.23-0.75). Expressive language and gross motor scales were lower than the population mean ($p \leq .001$) until 24 months, however gross motor skills improved while expressive language remained lower at 36 months. Gross motor skills were lower than fine motor skills at 6 and 12 months ($p \leq .001$), while expressive language was lower than receptive language at all timepoints ($p < .05$).

Conclusions: Prospective phenotyping from infancy allows for fewer biases and detailed analyses to characterize natural history in SCT. Expressive language and gross motor skills are known areas of risk in older children with SCT, and findings of deficits in these domains as early as 6 months of age implores further study and comparison of targeted interventions in infancy to determine those that change trajectory of neurodevelopment.

Keywords: XXY, XYY, XXX, developmental profile, speech, motor

21: Bias in Measurement of Autism Symptoms by Language Level and Nonverbal Mental Age in Minimally Verbal Children with Neurodevelopmental Disorders

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Background: Increasing numbers of children with known genetic conditions and/or intellectual disability are referred for evaluation of autism spectrum disorder (ASD), highlighting the need to refine autism symptom measures to facilitate differential diagnoses in children with cognitive and language impairments. Previous studies have reported decreased specificity of ASD screening and diagnostic measures in children with intellectual disabilities. However, little is known about how cognitive and language abilities impact the measurement of specific ASD symptoms in this group.

Methods: We aggregated a large sample of young children (age 31 to 119 months) to examine the measurement invariance of ASD symptoms among minimally verbal children within the context of the Autism Diagnostic Observation Schedule (ADOS) Module 1. Using confirmatory factor analysis (CFA) and moderated nonlinear factor analysis (MNLFA), we examined how discrete behaviours were differentially associated with the latent symptom domains of social communication impairments (SCI) and restricted and repetitive behaviours (RRB) across language levels and nonverbal mental age groupings.

Results: While the two-factor structure of SCI and RRB held consistently across language and cognitive levels, only partial invariance was observed for both ASD symptom domains of SCI and RRB. Specifically, four out of the 15 SCI items and one out of the three RRB items examined showed differential item functioning between children with "Few to No Words" and those with "Some Words"; and one SCI item and one RRB item showed differential item functioning across nonverbal mental age groups. Moreover, even after adjusting for the differential item functioning to reduce measurement bias across groups, there were still differences in ASD symptom domain scores across language levels.

Conclusions: These findings further underscore the influence of language level on ASD symptoms and the importance of measuring ASD symptoms within refined language levels, even among those with minimal verbal abilities.

Keywords: Autism Symptoms, Measurement Invariance, Language Level, Nonverbal Mental Age, ADOS

22. KEYNOTE: What Have We Learned from Psychiatric Genetics?

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The past decade has seen remarkable progress in elucidating the genetics of psychiatric conditions. However, these efforts reveal a complex picture that challenges our conceptualisation of these conditions and complicates the hoped-for translation into clinical practice. The previous dichotomy between rare syndromic conditions (like Fragile X or Rett syndrome) and the much more common idiopathic diagnoses of autism, schizophrenia, bipolar disorder, etc., has proven to be artificial. As more and more rare, high-risk mutations are found, it has become clear that these diagnoses represent umbrella terms, with massive genetic heterogeneity and overlapping aetiology. At the same time, variability in outcomes highlights the crucial contribution to risk of the polygenic background. Moreover, even in monozygotic twins, outcomes can be quite divergent, implying an important role for stochastic developmental variation in determining individual phenotypes. Finally, the genes implicated by rare or common variants do not point to specific biochemical pathways or processes. Instead, the processes of neural development are broadly and somewhat uninformatively implicated. Collectively, these results suggest a model where a general risk for neurodevelopmental dysfunction is conferred by rare mutations in any of possibly hundreds of genes; this risk is strongly modified by polygenic background, reflecting robustness of the system; and the phenotypes that emerge do not reflect the biochemical functions of the disrupted genes, but instead represent maladaptive attractor regimes of the dynamical neural system.

Keywords: neurodevelopment, robustness, heterogeneity, rare mutations, polygenic background, emergence

23. KEYNOTE: Gene Functional Impairment and its Correlation with the Phenotypic Profile of ASD in a National Cohort of UK Children with Intellectual Disability

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Background: Monogenic *de novo* mutations (DNM) are, cumulatively, an important cause of severe developmental disorders (DD), and many are associated with an increased risk of ASD. We aimed to test the hypothesis that there would be a significant association between specific functional groups of DNMs and the risk of ASD-related symptom clusters.

Methods: Children with DD of genetic aetiology drawn from IMAGINE-ID were enrolled from NHS Regional Genetics Centres throughout the UK (n=3400). We identified *de novo* causal variants in 808 participants, 4-19 years of age (49% female). Participating families completed a standardized psychiatric interview, measures of functional adaptation and behavioural/emotional adjustment. 202 genes with pathogenic *de novo* mutations, categorised into five functional groups: Gene Expression Regulation (GER); Neuronal Communication (NC); Cytoskeletal (Cyt): Chromatin Remodelling (CR); Other. ASD phenotypic characteristics were classified into clusters: socio-emotional reciprocity; non-verbal communication; developing relationships and repetitive stereotypic behaviours.

Results: ASD was diagnosed in 191 participants (32%) for whom sufficient clinical information was available. Prevalence by functional genetic disorder was 33% (GER & Cyt), 44% (ST), 38% (CR) and 23% (Oth). Adjusting for mental age revealed odds ratios for risk of ASD: 1.7 (GER), 2.5 (NC), 2.7 (Cyt) and 2.4 (CR) compared with Other gene functions. Overall, variation in gene function category was associated with socio-emotional reciprocity ($p<0.001$) and non-verbal communication ($p=0.04$) as well as with mental age ($p=0.02$) but accounted for only a small proportion of variance. Statistically significant differences did not survive adjustment for multiple testing.

Conclusions: There is currently growing interest in the relevance of genomic functions such as gene expression regulation and neuronal communication to potential differences in ASD symptom profiles. Our findings indicate that pathogenic DNMs in the categories NC, GER, Cyt and CR have a similar impact on the clinical features of ASD irrespective of their association with DD.

Keywords: Intellectual disability, autism, genetic disorder, metal health

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24. KEYNOTE: Reinforcement Learning and Social Attention in Rare Genetic Disorders: Results from the Swedish UNIKA Study.

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A major challenge in research about rare genetic disorders is the lack of easily administered and scalable methods for studies of ecologically valid behaviors. Here, I will discuss how novel use of eye tracking and mathematical modeling of behavior in conjunction with in-depth medical characterization can help us address this challenge.

The Swedish UNIKA study examines cognitive, social, affective, and medical aspects of rare genetic syndromes affecting brain development and function. I will present results from studies conducted in groups with Turner syndrome and Williams syndrome on two highly important behavioral functions in everyday life: reinforcement learning, and eye gaze processing. Reinforcement learning data were collected online, while participants completed the tasks in their own homes, while eye gaze processing was assessed in a research environment with a brief task which does not require verbal ability.

I will argue that these methods enable us to map syndrome-specific patterns of strengths and challenges in social behavior. The UNIKA study includes an in-depth genetic characterization including DNA analyses, RNA-based studies and establishment of an iPSC-NE model for WS (4 individuals). I will discuss promises and challenges linked to joint analyses of these data.

25. KEYNOTE: Neurocognition and Behaviour in Muscular Dystrophies

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Muscular dystrophies are a group of neuromuscular disorders associated with progressive weakness and loss of muscle mass due to abnormal genes interfering with the production of proteins needed to form healthy muscle. Symptoms may begin in childhood but depending on type of disease the first signs may not show until adulthood or late in life. Several bodily organs can be negatively affected and there exists scientific support for abnormal brain function in Duchenne muscular dystrophy and Myotonic dystrophy. This talk will give an overview of neurocognitive and behavioural abnormalities associated with these phenotypes, how they are manifested during life, and challenges in trying to understand the influence of genes on brain and behaviour. During the talk, results from cross-sectional and longitudinal studies performed at the Neuromuscular Centre, Sahlgrenska University hospital in Gothenburg will be presented.

Keywords: neuromuscular disorders, myotonic dystrophy, Duchenne muscular dystrophy, cognition, emotion

26. KEYNOTE: Changes in Mental Health, Quality of Life and Social Inclusion in Older Autistic Adults

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Background: Until recently studies of autistic adults were relatively few in number, and sample sizes and age ranges of participants were limited. Although research in this area is gradually increasing, findings remain inconclusive and there are no consistent data on whether difficulties in adult life tend to increase or improve with age.

Methods: Working with colleagues in the UK, the Netherlands and Australia, and using both cross-sectional and longitudinal designs, we have examined social outcomes, quality of life and mental health in several different cohorts of autistic adults with ages ranging up to 80 years. Comparisons were conducted between older and younger autistic adults and between older autistic and non-autistic adults. Factors associated with poorer or more positive outcomes were also investigated.

Results: Findings vary according to the ages and characteristics of the samples involved. Although, overall, autistic adults tended to face more difficulties and have a poorer quality of life than non-autistic peers, in several domains older autistic adults seemed to be more settled in their lives than previous studies of younger autistic adults had indicated. There were no specific variables that consistently predicted outcome although poor mental health has a significant impact on many aspects of functioning.

Conclusion: As research into the lives of older adults with autism has increased, earlier findings of very poor social outcomes and impaired quality of life appear to be less widespread than previously assumed. However, reliance on normative or "neurotypical" assessments of quality of life, and controversy over what constitutes a "good" social outcome, continue to pose challenges. Current studies highlight the need for co-produced research involving autistic adults from a wide range of backgrounds.

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27: The TAND Toolkit App – Participatory Development of a Mobile App to Reduce The Tsc-Associated Neuropsychiatric Disorders (TAND) Identification and Treatment Gap

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Background: TSC-associated neuropsychiatric disorders (TAND) include manifestations across behavioural, psychiatric, intellectual, academic, neuropsychological and psychosocial domains. Through ongoing participatory research with multiple stakeholders in the TSC community, various actions have been implemented to reduce the TAND 'identification and treatment gap'. One priority area was the development of a self-report, quantified app version of the TAND Checklist. Individuals and families also expressed the need for a 'toolkit' of evidence-informed advice, recommendations, and general intervention strategies that could allow them to manage TAND proactively, regardless of access to 'expert' clinical TSC care.

Methods: Over the last two years, the TAND Consortium, an international interdisciplinary group of 'lived' and 'technical' experts, have developed a self-report, quantified version of the TAND Checklist (TAND-SQ) embedded within a mobile app. This highly participatory study included three main aims: 1) development of the TAND-SQ into a mobile app, 2) development of consensus recommendations for identification and treatment of TAND, and 3) a range of networking and impact activities to strengthen the global TAND research community.

Results: In this presentation, we will outline the methodology used, the challenges identified related to technology development, and present some of the internal testing results that shaped the TAND Toolkit App into its current format ready for data collection. We will also demonstrate the app interface to show its utility in allowing users to capture their TSC story, complete the self-report, quantified TAND-SQ, and view their TAND clusters profile that indicates specific areas of difficulty and clinical need (e.g. eat/sleep cluster, mood/anxiety cluster). We will also outline next steps towards validation of the TAND-SQ, as well as app feasibility and evaluation.

Conclusion: Empowering families through technologies has the potential to establish a socially responsive, innovative telehealth paradigm for large-scale phenotyping that can inform large-scale self-guided intervention planning.

Keywords: Tuberous sclerosis complex, TSC-associated neuropsychiatric disorders, mobile app, telehealth, TAND Toolkit App, self-guided intervention

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28: Collaborating with the Global PWS Community to Better Understand Support and Advocacy Needs

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Background: Collaboration with people with disabilities has informed services that better meet people's needs in a variety of contexts. However, processes of self-advocacy for a number of communities whose disabilities are caused by the behavioural phenotype linked to their genetic neurodevelopmental disorder remain ad-hoc. A systematic evidence base that could encourage wide-spread adoption of services and systems designed together with these communities, for communities, is lacking. The global Prader-Willi syndrome (PWS) community is an example of one such under-served group. We aimed to collaborate with people living with PWS across the world to better understand their needs with respect to support and advocacy, using a process that could be documented and replicated to support widespread action.

Methods: Professionals and caregivers with experience of working with people living with PWS collaborated with research psychologists to design an online survey, which was discussed and refined in collaboration with people living with PWS. 78 adults with PWS from Argentina, Australia, Canada, China, France, Germany, Ireland, New Zealand, South Africa, Spain, Thailand, US, UK completed the survey. Content analysis was used to identify themes relating to support and advocacy needs. These themes were further expanded on by individual interviews with a sub-group of English-speaking participants from a number of countries.

Results: Themes identified from the survey were expanded on using reflexive thematic analysis of the interviews, to create a rich picture describing the needs and preferences of people living with PWS with respect to support and advocacy. The two-stage approach to data collection provided detailed descriptions, whilst still allowing the breadth of these views to be described.

Conclusions: The results provide a strong foundation for action that will support an active global community of people living with PWS working together with professionals and family members to improve the outlook for members of the community.

Keywords: Participatory design, co-design, intellectual disability, hyperphagia, emotional outbursts, advocacy

Abstracts for Poster Presentation

(in order of presentation)

POSTER 1: Functional Impact and Parental Wellbeing in the Context of Intellectual Disabilities of Known Genetic Origin

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Background: Parents' perceived Impact ratings capture the chronicity, distress and social impairment associated with children's emotional and behavioural problems. While it is well documented to be an important predictor of family well-being, less is known about parental appraisal of Impact for children with intellectual disabilities (ID) of genetic origin. Nor is the relationship between Impact and parental mental health clear within this population.
Methods: This study analysed data from 2423 children with ID of known genetic origin within the UK-wide IMAGINE-ID study. Factor analysis was conducted to examine the structure of the Strengths and Difficulties Questionnaire (SDQ) Impact supplement. We used structural equation modelling (SEM) to explore the links between Impact and parental well-being, and ask whether a child's genetic diagnosis, behavioural characteristics, demographic variables and family socioeconomic status (SES) influence Impact ratings.
Results: The Impact scale of the SDQ conforms to a two-factor solution in this population, comprising a home&distress dimension and a participation dimension. Parental well-being is strongly predicted by Impact:home&distress, but not Impact:participation. Life events, physical disabilities, and children's emotional, social and behavioural characteristics predict both Impact dimensions. Family structure, SES, and child's age predict Impact:home&stress. Examining the effect of genetic variant type (e.g. CNV or SNV), we found that genetic diagnosis indirectly influences parental well-being via Impact:Home&distress, but only within families who have recently received a diagnosis (within the previous two years).
Conclusion: We provide tentative support for a two-factor solution of functional impact among children with ID. Impact on home life and distress plays an important role within the family and further analyses are needed to understand dynamic relationships with child behavioural characteristics. Future studies should also consider examining and comparing the longitudinal influences on each aspect of Impact and their links to family adjustment in the context of genetic diagnosis.

Keywords: Intellectual disabilities; Genetic diagnosis; Functional impact

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POSTER 2: Neuropsychiatry: PharmacologicalInterventions for Neuropsychiatric Complications in DMD

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The association between Duchenne muscular dystrophy (DMD) and neuropsychiatric disorders has gained growing interest in scientific literature and clinical practice in the recent years. Frequency rates as reported in literature for ASD range from 3% to 32% and for ADHD from 12% to 50 %. Among the internalizing disorders, depression is reported in 17% to 27% of males with Duchenne muscular dystrophy, anxiety in 24% to 29% and obsessive-compulsive disorder in 5%.

As a consequence of the higher incidence of neuropsychiatric disorders in boys and young men with DMD, a multidisciplinary approach of diagnosis and treatment of these problems with neurological, psychological and psychiatric expertise is required.

The aim of this lecture is to illustrate the complex neurocognitive and neuropsychiatric comorbidities requiring precise and accurate pharmacotherapy and evaluation of effect for optimizing treatment in boys with DMD and neuropsychiatric comorbidity.

A group of 34 boys and young men with DMD and neuropsychiatric comorbidity, on psychopharmacological treatment, will be discussed.

Keywords: Duchenne Muscular Dystrophy, neuropsychiatric disorders, pharmacological interventions

POSTER 3: Autism Prevalence and Characteristics in Immigrant Communities in Minnesota

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Background: Previous research has demonstrated differences in prevalence and characteristics of autism across racial and ethnic groups. Higher prevalence and greater functional impairment have been found in immigrant children from low- and middle-income countries. At the same time, concerns have been raised about cultural bias in the diagnostic process. We have been tracking prevalence and characteristics of autism in Somali and Hmong children in Minnesota. Minnesota has the largest population of Somali immigrants, an estimated 57,000 people, and the second largest population of Hmong, close to 60,000 people.

Methods: We compared autism prevalence in 8-year-olds across racial/ethnic groups using data from the Minnesota site of the Centers for Disease Control and Prevention Autism and Developmental Disabilities Monitoring Network (MNADDM), with a focus on Somali and Hmong children. We also compared autism features and presence of co-occurring intellectual disability (ID) across racial/ethnic groups.

We combined data from 2014 and 2016 surveillance years to compare prevalence and characteristics across our populations. Prevalence calculations involved systematic review of health and education records of 8-year-old children within our defined surveillance area. Population denominators were obtained from census estimates for 2016 and adjusted to include only children in the surveillance area.

Results: Somali children had a higher autism prevalence than Hispanic children, while Hmong and Hispanic children had a lower autism prevalence than White children. White children had lower rates of co-occurring ID than Hispanic, Black (non-Somali), and Somali children, and clinician ratings of autism symptom severity differed by race/ethnicity.

Conclusions: Identifying subgroups of children with a higher prevalence or with greater support needs can inform public health policy and improve development for individuals with autism and their families. Differences by racial/ethnic group may suggest barriers to service access and utilization. Culturally informed methods for outreach and diagnosis are warranted to decrease disparities in evaluation and diagnosis of autism.

Keywords: autism, prevalence, cultural differences, health disparities

POSTER 4: Skill Attainment and Loss in Phelan-Mcdermid Syndrome

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Background: Phelan-McDermid Syndrome (PMS), a genetic condition involving SHANK3, is associated with profound intellectual and multiple disabilities, including severe motor impairments, absence of speech, and neurologic diagnoses such as epilepsy. Here, we describe skill attainment and loss among individuals with PMS, focusing on key developmental characteristics that may be tracked by paediatric providers in developmental monitoring.

Methods: Parent-reported information about the timing of milestone attainment was drawn from a prospective natural history study of children and adolescents with confirmed genetic diagnoses of PMS. Participants (N = 100) were between 3 and 20 years old (mean age 8.8 years; 54% male; 9% Asian, 2% Black, 85% White, 3% unknown race).

Results: Nearly all participants (97%) were able to walk independently, but the age at which this skill was attained was delayed for half of the sample (median [IQR]: 18 [15, 26] months). Non-attainment of language milestones was common: 34% did not attain single words and 61% never attained phrase speech. Of those who did attain at least single words, the age of onset was delayed (median [IQR]: 30 [24, 46] months). Language skills were also commonly reported as lost (24%). Of the entire sample, 39% reported probable or definite loss of other skills, most commonly babbling (35%) and responding to name (14%).

Conclusions: Individuals with PMS are likely to experience pervasive and widespread delays, and even non-acquisition, of important skills during development. Further, individuals with PMS who do acquire skills appear to be at increased risk of skill loss. Findings from this study will contribute to the dearth of information regarding the early development of individuals with PMS, informing healthcare providers, families, and other stakeholders of common developmental patterns seen amongst this population.

Keywords: milestone acquisition, skill loss, regression, language, motor, genetic conditions

POSTER 5: The Developmental Trajectories of the Behavioural Phenotype and Neuropsychiatric Functioning in Cornelia de Lange and Rubinstein-Taybi Syndromes: A Longitudinal Study

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Background: There is evidence that several neuropsychiatric disorders and changes in the behavioral phenotype arise with the growth of children affected by Cornelia de Lange Syndrome (CdLS) and Rubinstein-Taybi Syndrome (RSTS). However, previous research entirely relied on a cross-sectional study design turning into age-related comparisons of different syndromic cohorts to explore significant age-dependent changes in cognitive, behavioral, and mood aspects. We aim to outline the changing pathways of the behavioral phenotype and neuropsychiatric functioning across the lifespan in CdLS and RSTS, through the setting up of a longitudinal study design.

Methods: The sample included 14 patients with CdLS and 15 with RSTS recruited through convenience sampling. Cognitive, behavioral, and autism assessments were carried out at two different timepoints with Griffith's scales or the Leiter-R, the Child Behavior Checklist, the Child Autism Rating Scales, and Vineland Adaptive Behavior Scale-II.

Results: Our findings highlight that the cognitive profile of CdLS is subjected to a worsening trend with decreasing IQ/GQ scores from To to T1, whereas RSTS shows a stable IQ/GQ over time. Patients affected by RSTS show greater improvements compared to CdLS in expressive language, daily living skills, social abilities, and motor skills across the lifespan. Both syndromes report a downward trend in emotional and behavioral difficulties even if CdLS exhibit a significant and major deterioration compared to individuals with RSTS.

Conclusion: Being aware of the early dysfunctional patterns which might pave the way for later neuropsychiatric impairments is the first step for clinically intervening from a preventive perspective.

Keywords: Behavioural phenotype, Rubinstein-Taybi Syndrome, Cornelia de Lange Syndrome, longitudinal assessment, intellectual disability, rehabilitation

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POSTER 6: An Investigation on the Effects of Hormonal Replacement Therapy upon the Behavioral Phenotype of Males With 49,XXXXY

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Background: 49,XXXXY is a rare sex chromosome disorder, with an incidence of approximately 1:100,000. It has been associated with hypogonadism and heightened anxiety, thought problems, and externalizing problems. Hormonal replacement therapy (HRT) has been associated with improved neurodevelopmental outcomes in 47,XXY, specifically early hormonal treatment (EHT) and hormonal booster therapy (HBT). The current study investigates the effect of HRT on behaviour in children with 49,XXXXY.

Methods: Parents of 63 children with 49,XXXXY (CA: 112 months) completed the Child Behavior Checklist (CBCL). Participants were segregated based on HRT status: no-T (N = 22), EHT (N = 24), HBT (N = 6), and both EHT&HBT (N = 11). A one-way Analysis of Variance (ANOVA) was completed to determine group differences.

Results: No group differences were observed for demographic variables. The no-T presented heightened scores for externalizing problems compared to the EHT group ($p = .0015$) and for somatic complaints compared to the HBT group ($p = .041$). The EHT group showed decreased scores for somatic complaints and somatic problems in comparison to the HBT group ($p = .0082$, $p = .018$). Finally, the EHT&HBT group showed decreased scores for externalizing problems ($p = .0019$) compared to the EHT group, as well as for withdrawn/depressed ($p = .0061$), somatic complaints ($p = .00066$), internalizing ($p = .0048$), externalizing ($p = .044$), and somatic problems ($p = .0053$) compared to the HBT group.

Conclusions: This is the first study to explore the potential effects of HRT upon behaviour in 49,XXXXY. Externalizing problems and somatic complaints/problems were most significantly affected by HRT. Most notably, our findings suggest that the combination of EHT&HBT has a possible dosage-dependent effect in mitigating behavioural difficulties such that this treatment group performs better than those treated with only EHT or HBT. This study adds to the paucity of literature exploring behaviour in 49,XXXXY.

Keywords: 49,XXXXY, Neurodevelopment, Behavioural Phenotype, Hormonal Replacement Therapy

POSTER 7: Internalizing Problems in Children with Tuberous Sclerosis Complex

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Background: Children with tuberous sclerosis complex (TSC) are at risk of experiencing internalizing problems. These problems often precede more severe psychopathology, such as anxiety and mood disorders. However, research on this subject is still remarkably scarce. Therefore, we investigated the prevalence of internalizing problems in children with TSC. Also, we examined which factors were associated with more internalizing problems in children with TSC (such as intelligence level (IQ) or developmental level (DQ), age, and sex).
Methods: We assessed internalizing problem scores on the child behaviour checklist (CBCL) and intellectual or developmental levels (IQ/DQ) in a non-selected sample of children with TSC. Several hierarchical regression analyses were performed to examine the associations between internalizing problems and intellectual level. We included externalizing problems, age, sex, and the number of prescribed anti-epileptic drugs as control variables. Additionally, this study tracked symptom severity over two follow-up visits in our patient population, using paired sample t-tests.
Results: Elevated levels of internalizing problems were reported in almost 75% of the participating children. A significant model was found ($F = 10.53$, $p < .001$) in which externalizing problems ($B = .55$, $p < .001$) and age ($B = .28$, $p < .005$) were positively associated with internalizing problems in TSC. However, IQ was found to have no influence. Furthermore, internalizing problems tend to increase with age ($p < .001$), especially in female adolescents with TSC ($p = .03$).
Conclusion: This study indicated that children with TSC generally experience high rates of internalizing problems, and these problems increased over time, especially in female adolescents. Moreover, internalizing problems were indicative of higher rates of externalizing problems. Since these behaviours contribute to the burden of the disease, it is of great importance that all involved professionals are sensitive to internalizing problems.

Keywords: Tuberous sclerosis complex, Internalizing problems, Children, Adolescents, Female

POSTER 8: Caregivers of Children with ASD: What Determines Their Quality of Life?

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Background: This study investigated associations of the caregiver's quality of life (QoL) with several child, caregiver, and caregiving situation characteristics in 81 caregivers of clinically referred children (aged 2-10 years) with an autism spectrum disorder (ASD) classification. We included general and problem characteristics of the children and their caregivers, as well as caregiving situation characteristics.

Method: Data were collected as part of the "Social Spectrum Study", a prospective multicentre study focused on individual, familial, and societal characteristics of clinically referred children with autistic traits. We identified children with an ASD classification by using the Autism Diagnostic Observation Schedule (ADOS-2). Caregivers, mostly the parents, completed self-reports and proxy reports, also on potential caregiver resilience factors, such as adaptive coping and personal growth. Rather novel was the simultaneous assessment of health-related QoL with the EuroQol five-dimensional questionnaire (EQ-5D) and care-related QoL with the care-related QoL questionnaire (CarerQol) to capture both perspectives. We performed univariate and multivariable regression analyses.

Results: We found caregiver's health-related Qol to be associated with self-reported internalizing problems and adaptive coping, explaining 38% of the variance. Parenting stress and adaptive coping were associated with the care-related QoL, explaining 60% of the variance. Health- and care-related QoL each provided a unique perspective on the caregiver's QoL, with adaptive coping being a common factor. Child characteristics were not associated with the caregiver's QoL, if caregiver and caregiving characteristics were taken into account.

Conclusion: Findings indicate the importance of the caregiver's mental health, coping, and parenting stress in caring for and guidance of children with ASD.

Keywords: Autism Spectrum Disorders (ASD), Children, Caregiver's quality of life, EQ-5D, CarerQol, Coping

POSTER 9: IMAGINE-ID Personalised Research Reports: Understanding Participant's View of the Real-World Impact

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Background: Children and young people (CYP) with intellectual disability (ID) of genetic aetiology are at high risk of physical and mental health problems; IMAGINE-ID is a longitudinal UK cohort study (2015-2024) that measures emotional and behavioural adjustment with standardised assessments. To facilitate family participation, IMAGINE-ID created personalised reports for families on our findings, and sought feedback on the usefulness of these reports.

Methods: 1027 of the CYP's caregivers completed an online 'study impact' survey, with four subscales: i) shareability (report sharing); ii) utility (using report to obtain support, e.g., EHCP); iii) clinical (a change in clinical care); iv) psychological (a change in parental understanding of their child's behaviour). A global measure of Report Value was predicted from the subscale scores.

Results: 57.9% of participants (N=590) said they had shared their report with someone from outside the family. In total, the four subscale scores predicted 56.6% of the variance in Report Value ($F(4,1011) = 330$, $p<.001$, $R2=.566$). Families who considered it had greater Value emphasised its psychological impact ($\beta = 0.654$, $p < .001$), utility ($\beta = 0.08$, $p < .002$) and shareability ($\beta = 0.113$, $p < 0.001$). In contrast, clinical impact ($\beta = 0.06$, $p = .128$) was not a significant predictor of perceived Value.

Conclusions: Most families found the report provided valuable supporting evidence to share with others and that it improved their understanding of their child. Further analyses are needed to ascertain factors that differentiated those who did from those who did not find the report useful. Potential discriminating factors could include CYP characteristics (e.g., their degree of ID, severity of behavioural difficulties, level of current support etc.). A qualitative analysis of textual responses from families to our survey is underway, with a view to improving reporting during our 5-year follow-up study (2020-2024).

Keywords:
Intellectual Disability, Genetics, Research Impact, Participant Perspectives, Children and Young People

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POSTER 10: Reliability of the Vineland Adaptive Behaviour Scales Among Individuals with SCN2A

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Background: SCN2A-related neurodevelopmental disorders are due to pathogenic variants in the SCN2A gene, which codes for the voltage-gated sodium channel subunit alpha $Na_v1.2$, resulting in a spectrum of neurodevelopmental disorders characterized by severe developmental and epileptic encephalopathy and may include autism spectrum disorder. Monogenic conditions such as this are prime targets for future therapeutic interventions. Many individuals with SCN2A-related disorders exhibit severe developmental delays, making adaptive behaviour key meaningful outcomes. However, to be ready for such clinical trials, psychometric evidence for putative clinical outcomes and endpoints—including adaptive behaviour—must be established.

Methods: Families of children with SCN2A-related disorders were recruited through the FamilieSCN2A Foundation for a clinical trial readiness study. The project aimed to characterize the population and evaluate the reliability and validity of several caregiver-reported outcome measures. A subset of families was re-administered select measures after a target of 2 weeks to evaluate test-retest reliability. For 27 families, the Vineland-3 Comprehensive Interview Form was administered twice by trained research assistants, analysing change in growth scale values (GSVs), as appropriate for longitudinal research.

Results: $_R$etest occurred after a median of 22 days (IQR=13.5, range 14-70 days). All 11 subdomain scores exhibited a high level of reliability (median ICC=0.96, IQR=0.04). The lowest subdomain reliability was for Coping (ICC=0.48), while the highest was for Expressive Communication (ICC=0.99). The expected change in GSV scores normalized to a 2-week period was variable but within the standard error of measurement for the subdomains (median=-0.17, IQR=0.92, range -1.87-0.46).

Conclusion: The Vineland Comprehensive Interview exhibited a high degree of test-retest reliability with minimal change in scores. High test-retest reliability is key for clinical trials. In short periods of time, the GSVs are highly stable, but ongoing and future research is necessary to evaluate the natural history of adaptive behaviour among those with SCN2A-related disorders.

Keywords: SCN2A; Adaptive Behaviour; Reliability; Developmental and Epileptic Encephalopathy

POSTER 11: Don't Forget About Me: Dementia in Rare Genetic Neurodevelopmental Disorders, A Systematic Review

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Background: The lifespan of individuals with genetic intellectual disability (ID) has increased greatly over the last decades. This has exposed predispositions to health issues in adulthood for various genetic disorders, for example early onset Alzheimer's Disease in Down Syndrome. Early onset decline in cognitive functioning is also often seen clinically in other genetic disorders, but the association with the genetic background or other factors such as epilepsy or drug treatments is unclear. The aim of this systematic review is to study associations between genetic ID syndromes and cognitive decline in order to improve dementia recognition and care in this population.
Methods: A search was conducted in several databases. Search terms were related to dementia and genetic neurodevelopmental disorders in adults, the latter including generic search terms for neurodevelopmental disorders as well as an extensive list of rare genetic syndromes from the National Institute of Health. As studies on dementia were expected to be scarce, broader search terms on cognitive and adaptive decline were also included. This search yielded a total of 16226 articles to be screened. Title, abstract and reference screening reduced this to 199 full-text articles. This led to a total inclusion of 36 articles in 17 different syndromes, from which data was extracted. Cohen's kappa was calculated for interrater reliability.
Results: Results will be presented on reported clinical presentation of cognitive decline, and results of neuropsychological examination, in adults with genetic neurodevelopmental disorders. Validity of diagnostic methods, strengths and limitations of the studies will be reported. Qualitative and descriptive analyses will be performed.
Conclusion: Findings shall be discussed, providing recommendations to improve understanding and diagnosis of cognitive decline and dementia in adults with neurodevelopmental disorders.

Keywords: aging, intellectual disability, epilepsy, genetic syndromes, dementia

POSTER 12: Effects of Metformin on Individuals with Fragile X Syndrome and Additional Genetic Variants

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Background: While clinical characteristics may vary, most individuals with Fragile X syndrome (FXS) have speech/language delays and behavioural disturbances. Studies have suggested that metformin can improve speech/language, cognitive abilities, and behaviours. We report five cases of individuals with FXS and additional genetic variant(s) who experienced improvements in speech/language and behaviours after starting metformin.
Methods: Individuals with FXS and additional genetic mutations were trialled on metformin to evaluate its potential effects on speech/language and behaviours.
Results: 11-year-old boy with gain at 8p11.23, and losses at Xp22.33 and Xp21.3 who was speaking in phrases, and had daily outbursts and aggression was speaking in 5-7-word sentences, having back-and-forth conversations, and a decrease in aggression seven months after starting metformin 500mg daily. 11-year-old girl with deletion at 3p14.3 who had minimal spoken language, inattention, and frequent stimming behaviours was speaking in single words, had improved attention, and fewer stimming behaviours after starting metformin 500mg twice daily. 6-year-old girl with FXS related to a large deletion at Xq27.1q28 resulting in the loss of multiple genes had global delays and behavioural outbursts was speaking in full sentences and had fewer tantrum after starting metformin 400mg twice daily. 13-year-old boy with a deletion at 1q21.3 who spoke in phrases and had frequent behavioural outbursts was enrolled in a randomized control trial of metformin (group allocation has not been unblinded). At the conclusion of the study, he was started on metformin 500mg twice daily and three months later, he was speaking in 5–6-word sentences and had fewer outbursts. 20-year-old male with loss at 18p11.32 whose speech was limited to short phrases was speaking in 3–6-word phrases and reading sight words after starting metformin 500mg daily.
Conclusion: Individuals with FXS and additional genetic variants can have improvements in speech/language and behavioural disturbances with metformin.

Keywords: Fragile X syndrome, metformin, genetic variants

POSTER 13: Genetic Variants Identified in a Nonverbal/Minimally Verbal Cohort

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Background: The 2021 practise guidelines recommend exome/genome sequencing for individuals with neurodevelopmental delays (NDDs), such as autism spectrum disorder (ASD). While 30-40% of individuals with ASD have minimal spoken language, individuals who are nonverbal (NV) or minimally verbal (MV) are generally underrepresented or even excluded in many studies. There is currently limited literature on the developmental comes of these individuals. This study investigates the frequency of documented developmental assessments in a cohort of individuals who are NV or MV who have received whole genome sequencing.

Methods: Children and adults participated in a study evaluating whole genome sequencing (WGS) in individuals who are NV or MV with NDDs, with or without a related syndrome. NV was defined as having no consistent spoken words (intelligible or approximations). MV was defined as the ability to speak less than 50 words at 30 months and older. Study procedures included a clinical genomic evaluation where medical history and WGS was collected. Developmental assessments were abstracted from the medical record.

Results: Participants (37 M, 27 F) ranged in age from 2-38 years. A definitive underlying genetic cause was identified in 12 (18.8%) individuals. 7 individuals had variants associated with known genetic syndromes. 2 participants had documented cognitive evaluations and both had significant cognitive delays, consistent with the variants identified. 4 individuals had a diagnosis of ASD; 3 of these 4 individuals had multiple genetic variants.

Conclusion: WGS can assist with identifying disease-causing variants and aid in treatment plans and prognosis. Despite having limited speech/language skills, few of our participants had documented evaluations in other areas of development. Additional research is needed on the developmental outcomes of NV or MV individuals with associated genetic variants.

Keywords: genotype, phenotype, nonverbal, minimally verbal

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POSTER 14: Autism Spectrum Characteristics in Individuals with Monogenic Neurodevelopmental Disorders: A Comparative Data-Driven Gene Functional Network Approach.

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Background: Advances in next generation sequencing enable a genetic diagnosis to be identified in more than half of individuals with severe intellectual disability (ID). This facilitates exploration of links between aetiology and neurodevelopmental phenotypes, including autism spectrum characteristics (ASC). Previous research has shown that gene functional networks (GFN) - classifying rare monogenic causes of ID by molecular function - influences ASC. This study aims to replicate these findings in a larger independent sample, using a data-driven GFN classification approach.

Methods: Data regarding 152 children and adolescents (78 females, Mage = 118.91, SDage = 38.19) with monogenic diagnoses from a Simons Foundation Autism Research Initiative (SFARI) data registry, called Simons Searchlight, were included in this analysis. A gene ontology analysis approach was used to allocate genetic diagnoses to four GFNs: chromatin regulation, transcription factors, housekeeping/other functions and synaptic function. The dimensional structure of ASC in this population was mapped by applying Principal Components Analysis to the Social Responsiveness Scale. The hypothesis that GFN influences ASC was tested using Akaike Information Criterion (AIC) and multi-model inference. Models included demographic (age, gender) and non-ASC variables (adaptive function, anxiety and attention deficit hyperactivity disorder).

Results: PCA analysis identified four ASC components: (1) Social Relating and Communicating; (2) Sensory and Motor Flexibility; (3) Cognitive Flexibility; and (4) Social Confidence and Emotional Sensitivity. AIC modelling highlighted GFN as an important predictor of Components 1 and 2, but not 3 or 4. We identified contrasting relationships between adaptive function and Components 1 and 2 within different GFNs. Distinctive associations between variables were observed within the chromatin regulation group.

Conclusions: Consistent with previous findings we have shown that GFN predicts certain ASC dimensions but not others, and that GFN-specific pathways to ASC might exist, specifically for monogenic diagnoses affecting chromatin regulation.

Keywords : Neurodevelopmental disorders, Intellectual disability, Autism characteristics, Genetics

POSTER 15: Characterization of Cognitive, Language and Adaptive Profiles of Children and Adolescents with Malan Syndrome

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Background: Malan Syndrome (MS) is an ultra-rare overgrowth genetic syndrome due to heterozygous variants or deletions of the gene Nuclear Factor I X (NFIX). It is characterized by an unusual facial phenotype, generalized overgrowth, intellectual disability (ID) and behavioral problems. Even though limitations in cognitive and adaptive functioning have been previously described, systematic studies on MS cohorts are still lacking. Here, we aim to define the cognitive and adaptive behavior profile of MS children and adolescents, providing quantitative data from standardized evaluations.

Methods: 15 MS individuals were recruited and underwent evaluation with Wechsler Intelligence Scales, Leiter International Performance Scales and Griffith Mental Development Scales for cognitive profile and with Vineland Adaptive Behavior Scales-II Edition for adaptive functioning. Language skills and visuomotor integration abilities were assessed too. Comparisons and correlations between scales and subtests were performed.

Results: All the assessed MS individuals showed both a low cognitive and adaptive functioning. Among children and adolescents, 1 presented mild ID, 5 moderate ID and 8 severe ID. 1 patient received a diagnosis of psychomotor delay. Linguistic skills were impaired in all the individuals, with language comprehension relatively more preserved. Results revealed significant differences between VABS-II subdomains and strong relationship between cognitive and adaptive functioning.

Conclusion: All our cohort exhibited mild to moderate ID and adaptive behavior lower than normal, with Communication skills being the most affected. Regarding to Daily living skills domain, we interestingly found that scores on the Personal and Community subscales were dramatically lower than Domestic subdomain, highlighting the importance of considering behavior within developmental and environmental context. Our cognitive and adaptive MS characterization provides a quantitative a more accurate MS profiling, which is essential to help clinician to better understand the complexity if this rare disorder.

Keywords: Malan syndrome, NFIX variants, adaptive behaviour; cognition, sensory processing, intellectual disabilities.

POSTER 16: Parent Training Program Involving Families of Children with Noonan Syndrome: A Pilot Study

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Background: Noonan Syndrome (NS) is a rare genetic multisystem disorder caused by gene mutations involving the RAS/MAPK (mitogen-activated protein kinase) signaling pathway. It is characterized by typical dysmorphic facies, short stature and congenital heart defects. Psychomotor delay, learning difficulties and social deficits are also common. Furthermore, behavioral and attention problems can be reckoned as a key symptom in NS, with NS functioning resembling the patterns in ADHD (attention deficit hyperactivity disorder). This complex phenotype has great impact and causes demanding management issues also for patients' families. Parent training program (PTP) is recommended as first-line treatment for ADHD, however to date no studies have been performed to test the efficacy of PTP in NS. The aim of this pilot study was the implementation and evaluation of PTP in NS families.

Methods: 8 parents of children with NS were recruited and underwent to a 10-sessions of PTP. Three different questionnaires were administered to both parents in order to test the intervention's effects: on children challenging behaviors and ADHD symptoms with Conners Parent Rating Scales (CPRS); on parenting stress with the Parenting Stress Index Short Form (PSI-SF) and on parenting self-efficacy with the Alabama Parenting Questionnaire (APQ).

Results: Our preliminary data revealed that PSI-SF Parent-Child Dysfunctional Interaction, Difficult Child and Total scores decreased, while APQ positive parenting averagely increased in mothers after the intervention. Statistical analysis on fathers' questionnaires fulfilling did not show significant differences after the PTP sessions.

Conclusion: This pilot study suggests that PTP is a promising intervention for parents of children with behavioral and ADHD symptoms, such as NS individuals. Changes in mothers' attitudes and distress indicate that behaviorally oriented programs may help parents to manage with NS phenotype. Further experimental comparisons are yet required to confirm these encouraging data and to consider PTP a clinically validated intervention in NS.

Keywords: Noonan syndrome, ADHD, parent training, parenting stress, challenging behaviours, rare disease, evaluation program

POSTER 17: Evaluating the Difference in Neuropsychological Profiles of Individuals with FASD Based on the Number of Sentinel Facial Features: A Service Evaluation of the FASD UK National Clinic Database

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Background: It might be implied that those with FASD with fewer sentinel facial features have a "milder" neuropsychological presentation, or present with fewer impairments than those with more sentinel facial features.

Aim of the study: To compare the neuropsychological profile of people with FASD with varying numbers of sentinel facial features.

Method: A clinical sample of 150 individuals with FASD, aged between 6 and 37 years, completed a variety of standardised assessments as part of their diagnostic profiling. These included the documented level of risk of prenatal alcohol exposure (4-Digit Diagnostic Code), sensory needs (Short Sensory Profile), cognition (WISC-IV; WAIS-IV), and communication and socialisation adaptive behaviours (Vineland-II). The comorbid diagnostic outcomes of ASD and ADHD were also reviewed. Forty-two individuals (29 male, 13 female) were included in the 'FASD with 2 or more sentinel facial features' group, while the other 108 (50 male, 58 female) were in the 'FASD with 1 or fewer sentinel facial features' group. The profiles of the two groups were compared using Chi^2 tests, independent sample t-tests, and Mann-Whitney U analyses (where appropriate).

Results: There were no significant differences between the 'FASD with 2 or more sentinel facial features' and 'FASD with 1 or fewer sentinel facial features' groups across any measure included in this service evaluation.

Conclusion: Whilst sentinel facial features remain an important aspect in recognising FASD, our study indicates that there is no significant relationship between the number of sentinel facial features and the neuropsychological profile of people with FASD.

Keywords: FASD, FAS, Dysmorphology, Neurocognitive profile

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POSTER 18: Can We Make Personalised Care for Individuals With ID Happen? Insights from a Large ID Registry

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Background: With current techniques, a molecularly confirmed genetic diagnosis can be established in more than half of individuals with an intellectual disability (ID). There is increasing knowledge about the phenotype and treatments for genetic disorders. However, it is unclear to what extent the genetic diagnosis is integrated into multidisciplinary ID care. Knowledge and insight into this treatment gap can help improve integration of academic and ID care, and can help care providers with understanding and treating physical and mental health manifestations. We aim to investigate how often the genetic cause of ID is recorded in clinical files of various disciplines, including (ID) physicians, psychologists, behavioural therapists, and caregivers. Additionally, we aim to identify factors that are associated with integration of the genetic diagnosis in ID care to increase disorder-specific, personalised care.

Methods: The client database of 's Heeren Loo, a long-term care organization for people with ID, was searched. Medical records, care files used by behavioural scientists, psychologists, and professional caregivers were analysed for a sample of 374 (2.5%) out of 14,549 clients of all ages. The systems were searched for information on genetic diagnosis, clinical and demographic patient characteristics, types of support (e.g. involvement of caregivers), care package, and budget categories.

Results: The primary study parameter is the extent to which a genetic diagnosis was recorded in either medical files, psychological files or files used by professional caregivers. Associations between patient characteristics and presence of data on the genetic aetiology were investigated using regression analyses. Results will be presented.

Conclusion: Technological advances have contributed to the rapid progress in gene identification, with implications for understanding of the phenotype and personalised care for individuals with ID. Information on the genetic aetiology and associated phenotype will increase empowerment of families and health professionals, and improve well-being of the individual with ID.

Keywords: Intellectual disability, genetic, diagnosis, neurodevelopmental disorders, personalised, multidisciplinary care

POSTER 19: Deep Phenotypic Characterization in Patients with Neurodevelopmental Disorders and Their Non-Carrier Relatives to Investigate Causality of Rare Inherited Copy Number Variants

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Background: Copy number variants (CNV) inherited from a seemingly unaffected parent are typically disregarded in variant interpretation pipelines. However, understanding the contribution of these inherited CNVs to the phenotype is crucial for genetic counselling. An extended family-oriented approach is proposed, including deep familial phenotyping in intrafamilial carriers and non-carriers, to identify subtle or subclinical phenotypic expression of rare CNVS in relatives of the affected index patient. We performed deep familial phenotyping and multi-omics to interpret a rare paternally inherited 4q31 deletion in a boy with general developmental delay (DD).
Methods: Deep phenotyping (medical, developmental and behavioural, using standardized instruments) of carriers and non-carriers within the nuclear family, enables familial segregation analysis of a CNV with DD (sub)phenotypes. Trio whole genome sequencing is used to identify additional pathogenic variants causing or contributing to the phenotype. RNA and capture Hi-C sequencing on EBV cell lines is used to examine the CNV regulatory effect. This combined approach was applied to interpret a rare paternally inherited deletion ([GRCh37]4:141693186-142147039x1) in a 15-year-old boy with moderate intellectual disability, autism spectrum disorder, developmental coordination disorder, hypotonia and facial dysmorphic features.
Results: IQ-assessment revealed that CNV carriers scored lower on cognitive abilities than non-carriers: the index patient and his father had full-scale IQ (FSIQ) of 40(Pc.0.1) and 71(Pc.3) compared to the average FSIQs of mother (FSIQ 100,Pc.50) and sibling (FSIQ 92,Pc.30) respectively. The behavioural and adaptive profiles of carriers were more overlapping than profiles of non-carriers. De novo, recessive, X-linked and paternally inherited variant analyses of SNV, indels and additional CNVs were negative. RNA-seq shows four differentially expressed genes in the CNV or flanking regions (INPP4B,SETD7,MAML3,ZNF330). Their contribution to DD needs further study.
Conclusion: This multi-omics approach and correlation through deep familial phenotyping is suggestive of a contributory effect of this CNV to DD in this family.

Keywords: Deep familial phenotyping, Rare inherited CNV, Developmental disorders

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POSTER 20: Exploring Education for Children with 22q11.2 Deletion Syndrome: A Qualitative Study of Parents Perspectives

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Background: 22q11.2 deletion syndrome (22qDS) is a complex and widely variable syndrome including intellectual disability, the presence of social-communication difficulties, and mental health issues, all of which impact upon learning and peer relationships within educational contexts. Some research indicates that children with 22qDS struggle with learning and attending school. To explore this, we invited parents to discuss their child's learning experience within educational contexts.

Methods: We conducted 3 online focus groups and 1 online semi-structured interview with a total of 9 mothers of children diagnosed with 22qDS. Parents were included if their child (a) had a formal diagnosis of 22qDS, and (b) was aged from 2 – 12 years old. The Mothers were asked a series of open-ended questions to explore the educational experiences of their child with 22qDS.

Results: We adopted an inductive approach to our data analysis and conducted a reflexive thematic analysis resulting in the emergence of five major themes (1.) The impact of 22qDS on classroom-based learning; (2.) The educational setting; (3.) The parent role in their child's learning; (4.) Educational progression; and (5.) The impact of adaptive behaviour skills on learning experiences. From these themes, 11 sub themes were identified. Parents reported that health issues impacted upon their child's participation in learning, the educational setting often negatively impacted upon learning, parents reported a lack of confidence in supporting their child's learning, and specific adaptive behaviours, like toileting, were significant barriers to their child's learning.

Conclusion: Results from this study highlight aspects of education where children with 22qDS require (a) increased and flexible support that is tailored to their specific needs, and (b) a greater understanding from educators of the child needs, and the parents' expectations within learning contexts. Furthermore, as their child progressed from preschool to primary school, parents perceived the level of support provided diminished.

Keywords: Learning, DiGeorge syndrome, Velocardiofacial syndrome, rare genetic syndrome, parents, schooling

POSTER 21: Early Childhood Biomarkers of Behavioural Difficulties and the Associated Influence of Early Androgen Therapy in Males With 47,XXY, Klinefelter Syndrome

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Background: 47,XXY, Klinefelter syndrome, is the most common X and Y variation (1:650) and is characterized by androgen deficiency and increased levels of anxiety, attentional difficulties, and other behavioural complications. Recent research demonstrates that early hormonal treatment (EHT) may mitigate symptoms of anxiety and behavioural problems among males with 47,XXY. This study identifies early biomarkers of behavioural dysfunction among untreated young children with 47,XXY and explores the potential impact and benefits of EHT on the behavioural phenotype. We hypothesize that EHT may improve behavioural functioning and therefore strengthen the relationship between neurodevelopment and androgen deficiency.

Methods: Parents of 223 boys with 47,XXY between 1 month and 6 years old (CA 37.7 months) completed the Child Behavior Checklist (CBCL) and the Behavior Rating Inventory of Executive Function years Preschool questionnaire (BRIEF-P). Subjects were segregated into two groups: 46 no-T and 177 EHT. Independent samples *t*-tests were utilized to assess group differences.

Results: On the CBCL, boys who received EHT had significantly lower scores in emotional reactivity (P=0.001), withdrawn (P=0.016), sleep problems (P=0.009), attention problems (P=0.005), aggressive behaviour (P<0.05), internal problems (P=0.002), external problems (P=0.002), total problems (P=0.002), affective problems (P<0.05), anxiety (P=0.003), pervasive-developmental problems (P=0.005), attention deficit/hyperactivity (P=0.001), and oppositional defiant problems (P<0.05).

On the BRIEF, boys who received EHT had significantly lower scores in shift (P=0.02), emotional control (P=0.003), inhibitory self (P=0.02), and flexibility (P=0.004).

Conclusion: The present study indicates that EHT may have considerable positive impacts on behaviour among children with 47,XXY under 6 years old. Many problematic behaviours characteristic of boys with 47,XXY, such as anxiety, depression, and ADHD symptomatology, were significantly improved in association with the administration of EHT in this study. Identifying how the behavioural phenotype of 47,XXY evolves with age is critical to understanding the diagnosis and mitigating further behavioural problems that surface later in life.

Keywords: 47,XXY, Klinefelter syndrome, early hormonal treatment, behaviour, anxiety

POSTER 22: Psychological Effects of Testosterone Therapy in Tanner 2-3 Males with XXY: Results of a Randomized, Placebo-Controlled Trial

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Background: Most adolescent males with XXY/Klinefelter syndrome develop testosterone deficiency during puberty leading to the need for testosterone replacement therapy. Clinical questions frequently arise related to the effects on testosterone replacement on internalizing and externalizing behaviours, mood, cognitive skills, executive functioning (EF) and self-esteem. This study aimed to investigate these questions using a double-blind, placebo controlled study design.

Methods: Forty-nine Tanner 2/3 males with XXY were randomized to receive testosterone 1% (T) or placebo gel (P) daily for 12 months; 44 completed the study (n=26 testosterone; n=18 placebo). Direct performance-based assessments, questionnaires (parent and self report), and clinician impression measured domains of cognitive skills, EF, behaviours, and self-esteem at baseline and 12 months. Factor analysis allowed creation of composite scores for each domain. Independent-samples t-tests compared baseline scores in each domain between treatment groups and one-sample t-tests compared the total cohort to standardized norms. Repeated measures ANOVAs assessed testosterone treatment effect. Effect sizes on difference scores were calculated.

Results: The study cohort showed variability and differences in all domains compared to norms, consistent with prior literature. Treatment groups were well-matched on age (p=0.99), full scale IQ (T 86.7sd16.4 vs P 82.8sd13.7; p=0.44), maternal education (p=0.89), and race (p=0.67). Testosterone neither significantly worsened nor improved cognitive skills (verbal IQ, nonverbal IQ) or EF, but small effect sizes were noted in EF subdomains for inhibition (Cohen's d = 0.3/0.2), planning/switching (Cohen's d = 0.3) and attention (Cohen's d = 0.3). Results of behavioural domains and self-esteem will be presented.

Conclusions: Testosterone therapy for 12 months in early puberty does not lead to improvement in verbal or nonverbal cognitive scores. Effect sizes of some EF subdomains support mild improvement. Results of randomized, placebo-controlled trials are needed to guide evidence-based treatment guidelines.

Keywords: XXY, Klinefelter syndrome, testosterone

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POSTER 23: Epigenetics in Neurodevelopmental Disorders

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Background: Autism spectrum disorders (ASD) is a heterogeneous developmental disorder, with about 70% of cases due to unknown aetiology. Among the monogenic causes of ASD, Fragile X syndrome (FXS) accounts for 2-4% of ASD cases and 60% of individuals with FXS present with autism. Epigenetic changes, specifically DNA methylation, which modulates gene expression levels, plays a significant role in the pathogenesis of both disorders. Of importance also the gut microbiota can influence epigenome.

Methods: Global DNA methylation profiles of biological samples derived from 57 age-matched male participants (2-5 years old) including 23 subjects with ASD, 23 subjects with FXS with ASD and 11 typical developing children were obtained. Human Methylation EPIC Bead Chips, including 850,000 CpG sites throughout the genome, were used for this study. Further we have also investigated 17,735 CpG sites spanning the whole mouse genome, we characterized the epigenetic profile in two cohorts of mice descended from mothers treated and non-treated with *Lactobacillus Reuteri* to determine the effect of prenatal probiotic exposure on the prevention of the observed FXS-like behavioural and symptoms.

Results: In both studies, we found several genes involved in different neurological pathways being differentially methylated ($P \leq 0.05$) between the groups. Among the key functions, synaptogenesis, neurogenesis, synaptic modulation, synaptic transmission, reelin signalling pathway, promotion of specification and maturation of neurons and long-term potentiation were observed.

Conclusions: This preliminary study identified a significant role of altered DNA methylation in the pathology of ASD and FXS, suggesting that the characterization of a DNA methylation signature may help to unravel the pathogenicity of FXS and ASD and may help the development of an improved diagnostic classification of children with ASD and FXSA. In addition, it may pave the way for developing therapeutic interventions that could reverse the altered methylome profile in children with neurodevelopmental disorders.

Keywords: Fragile X, Autism, Epigenetics, Microbiota, Intellectual Disabilities, Methylation

POSTER 24: Delayed Motor and Language Milestones and Later Functional Impairment in Probands with Genetic Conditions from SFARI Registries

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Background: The age of attaining developmental milestones, such as walking and talking, is one way to quantify very early aspects of the phenotype of genetic conditions. In previous work, we reported that delays in major developmental milestones, particularly in gross motor skills, are frequent and may be among the earliest indicators of differentially affected developmental processes in several rare genetic conditions associated with autism spectrum disorder and other neurodevelopmental disabilities. In this study, we focus on the relationship between milestone attainment and later functional impairment within these conditions.

Methods: Simons Searchlight registry participants aged 3–40 years old were included if they had a confirmed genetic diagnosis (copy number or single nucleotide variant) and a valid Adaptive Behavior Composite (ABC) score from the Vineland-II Adaptive Behavior Scales (interview form). Within each subgroup, parent-reported ages of acquisition of three gross motor (sitting, crawling, and walking) and two expressive language (first words and first phrases) milestones were categorized relative to normative expectations.

Results: The proportion of the subgroup with ABC less than 70 was high across most conditions, including ≥67% of each of the 12 monogenic conditions and between 13% and 48% for each of the four copy number variant conditions. The rate of delay, especially for motor milestones, was generally high; for all conditions, at least one milestone was delayed in >50% of the subgroup. Delay in walking was most strongly related to ABC category. Across all conditions, delayed walking occurred for 174/226 (76.9%) with ABC<70, compared to 53/114 (46.4%) with ABC>70.

Conclusion: This study further confirms a strong relationship of early motor delays to later indices of intellectual disability in children with specific genetic conditions. Greater understanding of how the age of attainment of certain milestones is related to later functioning may help clinicians in sharing prognostic information with families.

Keywords: Milestone acquisition, language, motor, genetic conditions, adaptive behavior

POSTER 25: Deep Phenotyping in 38 patients with Proximal 22q11.2 Duplications

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Background: Microduplications on chromosome 22q11.2 are associated with a variety of phenotypes, including both clinical and developmental features and a high rate of familial transmission. This study contributes to the characterisation of the clinical and neurodevelopmental phenotype of this recurrent Copy Number Variant (CNV).
Methods: We analysed digital medical records of 38 patients (median age = 14.8 years, 17 female and 21 male) carrying proximal 22q11.2 duplications in order to characterise clinical, neurodevelopmental and behavioural features, including longitudinal data in a subgroup (*n=17*). Phenotypes of *de novo (n=12)* and *inherited* (*n*=19) duplications were also compared.
Results: Common clinical features include nutritional problems (59%), transient hearing impairment (50%), congenital heart defects (29%) and neurological abnormalities (44%). Developmental delays are reported in early infancy, whereas learning (64%), attention (64%), speech-language (56%) and motor problems (56%) are present from primary school age on. The most common neurodevelopmental disorder is Attention-deficit/hyperactivity disorders in 33%. Average full-scale intelligence quotient (FSIQ) is 77 in the borderline range (FSIQ 70-84), with 23% of patients showing mild intellectual disability (FSIQ 55-69). Longitudinal IQ-data in a subgroup of patients (n=17) indicate that 53% show a growing into deficit trajectory with increasing age. No significant differences in phenotypes were observed between the *inherited* and *de novo* 22q11.2 duplication group, apart from a trend towards more failure to thrive in the latter.
Conclusion: In this study, we confirm a highly variable clinical, developmental and behavioural phenotype in patients with proximal 22q11.2 duplications, and provide for the first time longitudinal IQ-data. Only index patients with medical or cognitive problems were included, potentially resulting in an ascertainment bias. Therefore, future studies should also include family members with 22q11.2 duplications diagnosed through segregation analysis. Finally, these findings are relevant to medical and mental healthcare professionals and may help to guide medical and neurobehavioural follow-up.

Keywords: 22q11.2 duplication, copy number variants, deep phenotyping, Neurodevelopmental Disorders, developmental trajectories

POSTER 26: Overweight, Obesity and Assessment of Food Related Problems in Italian Individuals with Intellectual Disability

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Background: Intellectual Disability (ID) shows 1-3% prevalence in the general population. Subjects with ID have a significant risk of developing overweight, obesity, nutritional-related chronic disease and eating related disorders. Therefore, the aim of our study has been to evaluate the relationship between ID, nutritional assessment, and the presence of eating related disorders in an Italian cohort of patients affected by this condition.

Methods: The experimental plan included a recruitment time (To), when sixty-one subjects were contacted and their Intelligence Quotient (IQ) has been evaluated; at a second time (T1), the patients scored ≤ 80 have been selected and we estimated their aetiology, their life-style and their anthropometric and psychometric parameters. Wechsler Scales measured the Intelligence Quotient; anamnesis defined lifestyle and aetiology. Body Mass Index (BMI) and Waist to Hip Ratio (WHR) estimated nutritional assessment. The Eating Attitude Test (EAT26) and the Food Relating Problems Questionnaire (FRPQ) assessed eating related disorders. Data statistical analysis methods were X square, ANOVA and post hoc Bonferroni's test.

Results: Into the sample, we estimated fifty-two intellectually disabled, with different degrees and with a genetic or idiopathic aetiology. Most of subjects were overweight or obese. We estimated different levels of obesity and a correlation between degree of ID, nutritional assessment and eating habits. Many subjects showed eating related disorders, correlated to genetic diagnosis, overweight or obesity and IQ score.

Conclusions: Overweight, obesity and eating related disorders are very common among intellectually disabled. A multidisciplinary approach must be used for these patients.

Keywords: Intellectual disability, obesity, Food related problems

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POSTER 27: Traces of Impaired Social Communication and Cognitive Performance in the Brain of Children with Neurodevelopmental Disorders

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Background: Most neurodevelopmental disorders have complex and multiple contributors and typically emerge during childhood, a period involving substantial brain development. The interplay of such contributors and how they relate to neurodevelopment is not well understood.

Methods: We used canonical correlation and independent component analysis to model associations between brain structure, cognitive, clinical, and environmental variables, using data from the Healthy Brain Network. The sample consisted of youth aged 5-21 from New York City, USA (n = 1732, 64% male), with the following diagnosis categories: ADHD: 752; other neurodevelopmental disorders: 390; anxiety: 267; mood: 63; other disorders: 67; no diagnosis: 188. Then we performed out-of-sample validation of the detected brain-patterns in the Philadelphia Neurodevelopmental Cohort (PNC), an independent sample of largely undiagnosed youth aged 8-21 (n=1253, 54% female).

Results: We identified two modes of brain-behaviour covariation. The first mode linked age, physical and cognitive maturation to brain features including reduced cortical thickness and gyrification (r=.92, p=.005). The second mode linked lower language skills, lower academic performance, trouble with social communication and psychological difficulties, including attention problems and externalisation (r=.92, p=.006), with lower white matter surface area and gyrification. Youth with a diagnosis of ADHD or other neurodevelopmental disorders showed elevated scores for this pattern compared to their non-diagnosed peers (beta=.68 and beta=.57, respectively, both p<.0001). Out-of-sample validation replicated the covariation pattern across brain features for both modes in PNC. The first brain pattern correlated highly with age and age-related cognitive maturation, while the second brain pattern was most strongly associated with deviations from normative cognitive development.

Conclusion: Our results link socio-cognitive difficulties to brain structure in children with neurodevelopmental disorders. The replication of this pattern in an undiagnosed sample underscores the importance of cognitive development for neurodevelopmental trajectories of health and disease.

Keywords: Multivariate, neurodevelopment, brain structure, cognition, normative cognitive deviation

POSTER 28: Post-Traumatic Stress in Adults with 22q11.2 Deletion Syndrome

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Background: Patients with 22q11.2 deletion syndrome (22q11.2DS) have an increased risk of schizophrenia and other psychiatric disorders. Counterintuitively, the prevalence of post-traumatic stress disorder (PTSD) has been reported to be much lower compared to the prevalence in the general population; 0.9% in 22q11.2DS vs 3.9%. We hypothesized a higher prevalence of PTSD, and studied potential predictors to PTSD, in adults with 22q11.2DS.
Methods: We reviewed medical records of 112 adults (mean age 32.5±12.4 years, 45% male) who visited the Dutch specialty clinics for adults with 22q11.2DS at Maastricht University Medical Centre+ and/or 's Heeren Loo up to 2021. Prevalence of a clinical PTSD diagnosis, a traumatic event defined as exposure to actual or threatened death, serious injury or sexual violence, and other potentially traumatic events affecting daily functioning, were calculated. A logistic regression analysis was used to explore associations between sex or full-scale intelligence quotients (FSIQ) and PTSD.
Results: Nine patients (8.0%, 95% confidence interval: 3.0%-13.0%) had a history of PTSD, of whom two were referred for trauma-related problems. A traumatic event was experienced in 23 patients (20.5%): 12 (10.7%) sexual violence, 11 (9.8%) serious injury, and 4 (3.6%) actual or threatened death. An additional 17 patients (15.2%) experienced other potential traumatic events, including bullying (13; 11.6%) and multiple hospitalizations/ surgeries (4; 3.6%). Treatment for trauma was reported in 20 patients (17.9%), of whom 8 with PTSD. Neither sex nor FSIQ was associated with PTSD ($p>0.05$).
Conclusion: PTSD and other traumatic events appear to be prevalent in adults with 22q11.2DS. Clinicians should be alert to PTSD in 22q11.2DS in order to minimize psychiatric burden with reduced quality of life. Systematic studies in individuals with 22q11.2DS are needed to improve diagnosis, including attention for seemingly innocuous life events that may be traumatic.

Keywords: Post-traumatic stress disorder, trauma, 22q11.2 deletion syndrome, intellectual disability, adults

POSTER 29: Unpicking the Drivers of Neuropsychiatric Risk in Children with Autism Spectrum Disorders that are Associated with Intellectual Disability

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Background: Children with a developmental disability (IDD) are at increased risk of poor mental health compared with typically developing children. We hypothesised the families of those with ASD in addition to IDD would experience greater psychological stress.

Methods: Participants with IDD caused by either a copy number variant or single nucleotide variant (5-19 years) were recruited via the UK National Health Service. 1904 caregivers competed an online assessment of their child's mental health and reported on their own psychological wellbeing. Using standardised interviews and questionnaires, we assessed the severity of behavioural and emotional difficulties, both in children with IDD alone and in those with co-occurring ASD. We then examined their association with parental psychological distress, adjusting for children's sex, developmental level, physical health, and the families' degree of socio-economic deprivation.

Results: 701 (36.8%) had co-occurring ASD. Children with IDD and co-occurring ASD had more mental health diagnoses (ADHD: OR=1.84, 95%CI 1.46 to 2.32, p<.0001 ; emotional disorders: OR=1.85, 95%CI 1.36 to 2.5, p<.0001 ; disruptive behaviour disorders: OR=2.04, 95%CI 1.56 to 2.68, p<.0001) and mental health difficulties (hyperactivity: B=0.25, 95%CI 0.07 to 0.34, p=.006; emotional difficulties: B=0.91, 95%CI .67 to 1.14, p<.0001 ; conduct problems: B=0.25, 95%CI .05 to 0.46, p=.013) in fully adjusted models. Parents of children with IDD and ASD reported greater psychological distress (B=1.5, 95%CI .85 to 2.21, p<.0001) but not after adjustment for co-occurring child mental health difficulties (B=0.4, 95% CI -0.27 to 1.1, p=0.24)

Conclusions: Children with IDD of genetic cause and co-occurring ASD had more severe, and a wider range of mental health difficulties compared to those with IDD alone. Parents of these children experienced more psychological distress; this was accounted for by their child's co-occurring mental health difficulties and may reflect a need for increased support.

Keywords: Intellectual disability, autism, genetic disorder, mental health

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POSTER 30: What is the Impact of Shielding on Children and Young People in IMAGINE-ID During the Coronavirus Pandemic?

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Background: IMAGINE-ID is a UK cohort study of children and young people (CYP) (6-26 years) with intellectual disability (ID) of genetic aetiology. Due to their complex physical health presentations, they were more likely to have been shielding than the general population during the COVID-19 pandemic.
Methods: 1063 caregivers completed the Strengths and Difficulties Questionnaire (SDQ) and the Coronavirus Health and Impact Survey (CRISIS) between May-December 2021.
Results: CRISIS responses indicated that 40.5% (n=431) of caregivers reported that their child had been shielding during the pandemic. CYP who had been shielding had significantly higher scores on the SDQ emotional problems subscale (p=.002); and significantly lower prosocial ability subscale scores (p<.001) compared to those who were not shielding. There were no significant group differences between scores on the SDQ conduct problems, hyperactivity or peer problems scales.
Overall 84.5% (n=898) of CYP faced challenges due to the pandemic. The most commonly reported challenges were social distancing (n=256; 24.1%), anxiety (n=229; 21.5%), loneliness (n=146; 13.7%) and low mood (n=71; 6.7%). There was no association between the reported biggest challenge and shielding status (p=.5).

Conclusions: CYP experienced a range of challenges during the pandemic. Those who were shielding were reported to have greater emotional difficulties and worse prosocial skills than those that did not shield. Our analysis did not control for pre-pandemic SDQ scores. Further analyses are needed to establish whether emotional and pro-social difficulties were associated with shielding behaviour, or associated with the characteristics of those that choose to shield.

Keywords: Intellectual disability, mental health, behaviour, genetics, Covid

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SSBP Syndrome Sheets 2022

The SSBP hopes that readers will find the syndrome information sheets useful. They represent the views of the authors who kindly prepared them, and not necessarily those of the SSBP.

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).

Websites:

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

- www.nas.org.uk

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- 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

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Coffin Siris

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..

Neuropsychological characteristics

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

Available guidelines for behavioral assessment/ treatment/management

Frequent infections have been reported for individuals diagnosed with Coffin Siris syndrome. Respiratory infections may be related to hypotonia, poor sucking, and aspiration besides increased susceptibility. Consultation with feeding clinics, G tube placement, fundoplication, thickened infant feedings, and careful positioning post-feeding may be helpful. Early cardiac evaluation is suggested. Indications for surgical or

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

Useful Websites

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

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

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, 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, cardiac and genito- urinary problems. Gastro-intestinal disorders are particularly problematic in CdLS.

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-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 compulsive like behaviours within the syndrome such as tidying up and lining up behaviours (Hyman *et al.*, 2002; Moss *et al.* 2009) also indicates that individuals with CdLS may be at risk for difficulties with behaviour regulation.

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 (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 and generalised anxiety (Crawford, Waite & Oliver, 2017; 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 (Goodban, 1993; Groves *et al.*, 2019); 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 Reid *et al.* (2017) and Johnson (2015) demonstrated impairments in aspects of executive function including impairment on tasks requiring generativity (verbal fluency), cogntive flexibility but with inhibition and working memory representing relative strengths. Reid *et al.* (2017) also demonstrated that verbal working memory (backwards digit span) and verbal fluency skills were significantly negatively correlated with chronological age in CdLS but not a contrast group of individuals with DS, indicating increased deficits in these areas with age.

Age related change

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

Available guidelines for behavioural assessment/ treatment/management

- Kline, A., Moss, J., Selicorni, A., Bisgaard, A-M., Deardorff, M., Gillett., P, *et al.* (2019). *Diagnosis and management in Cornelia de Lange Syndrome: First international consensus statement.* Nature Reviews Genetics. 19(10), 649-666.
  Summary available from: https://www.cdlsworld.org/xwiki/bin/view/cdlsPublications/consensus/
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Useful websites/associations for more information

- CdLS Foundation UK and Ireland: www.cdls.org.uk
- CdLS World: www.cdlsworld.org
- FIND resources: www.findresources.co.uk
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J Moss & C Oliver, July 2010.

Updated: J. Moss, L. Nelson & C. Oliver, July 2015

Updated: L. Groves, J. Moss, & C. Oliver, July 2019

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 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

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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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P Tunnicliffe, J Moss, & C Oliver, July 2015
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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 (DS) by Jérôme Lejeune, Raymond Turpin and Marthe Gautier in 1959 (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 DS (de Graaf, Buckley, & Skotko, 2015). 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 DS (Wu & Morris, 2013) however in Iceland, no infants with DS have been born during a five year period (Wise, 2016).

The likelihood of having a child with DS 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 (Englund, Jonsson, Zander, Gustafsson, & Annerén, 2013). While rare, it is not unheard of for some individuals to live past the age of 70. This means the numbers of individuals with DS are increasing, despite prenatal testing.

Genetics

DS is caused by a third copy of human chromosome 21 (Hsa21) (Lejeune *et al.*, 1959). This is typically a full or partial trisomy of Hsa21, however translocation whereby a section of Hsa21 has attached to another chromosome (most commonly the long arm of Hsa21 to Hsa14 or Hsa22) or mosaicism, in which the third copy of Hsa21 is present in some, but not all of an individual's cells, account for around 4% and 1.3-5% of the DS population respectively (Flores-Ramírez *et al.*, 2015; Morris, Alberman, Mutton, & Jacobs, 2012; Papavassiliou, Charalsawadi, Rafferty, & Jackson-Cook, 2015).

This excess of genetic material leads to a 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).

230 coding, and 404 non-coding genes have been identified on Hsa21 (Ensembl, 2018). It remains a subject of on-going research whether DS specific phenotypes and disease suscepitibility are the result of general dysregulation of the genome caused by the presence of aneuploidy, or whether they are related to gene-specific over expression. Some diseases, such as early onset Alzheimer's disease (AD), appear directly linked to the presence of an additional copy of a gene, in this case APP. Duplication of the APP gene in the absence of DS is known to be sufficient to cause early onset AD (Sleegers *et al.*, 2006). However, in mouse models it has been shown that triplication of other Hsa21 genes may also increase amyloid deposition (Wiseman *et al.*, 2015, 2018).

The development of mouse models 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 DS phenotype. Models are used to show whether specific genes are necessary and sufficient to cause a certain phenotype.

Genes that have been identified which appear to contribute to the DS phenotype include dual specificity tyrosine-regulated protein kinase 1 (DYRK1A), DSCR1, BACE 2 and GATA 1:

DYRK1A is particularly expressed in the hippocampus, cortex ,cerebellum, and heart—regions affected in DS and overexpressed in fetal DS. Transgenic mice that overexpress DYRK1A show learning and memory deficits. Further, DYRK1A phosphorylates tau protein, and this change is known to be important in initiating the cascade of processes leading to amyloid formation in AD. When this over-expression is reduced in these mice, amyloid-beta and tau levels are reduced, as is cholinergic

neurodegeneration (García-Cerro, Rueda, Vidal, Lantigua, & Martínez-Cué, 2017)

DSCR1 is overexpressed in AD patients and causes abnormalities in synapse function in DS individuals. DYRK1A and DSCR1 act synergistically to regulate the transcription factor NFATc, which plays a critical role in the development of the central nervous system (Einfeld & Brown, 2010).

BACE 2 expression has been linked in some studies to the development of AD and age of onset in the DS population, although results have been inconsistent (Mok *et al.*, 2014).

Mutations in the GATA1 gene have been associated with the development of transient myeloproliferative disorder and megakaryoblastic leukemia of DS in conjunction with trisomy 21 (Groet *et al.*, 2003).

Physical and Mental Health

There is considerable variation in the penetrance of the phenotype associated with trisomy 21, however certain characteristics are more common. For example, intellectual disability is present to some degree in all patients with full trisomy 21, as is muscle hypotonia and AD neuropathology after the age of 35 years (Antonarakis, Lyle, Dermitzakis, Reymond, & Deutsch, 2004). Motor dysfunction is highly prevalent among individuals with DS, who can exhibit clumsy sequences of movements, and poor control in programming motor sequences, their timing and force. Motor dysfunction in DS is accompanied by hyporeflexia and reduced muscular strength and tone (Dierssen, 2012). Most adults with DS are of short stature (70%), with a characteristic facial appearance. The eyes seem to slope upwards and outwards as a result of alterations in the structure of the surrounding tissues. The nose has a wide bridge, and the head an unusual shape ("brachycephaly"). Protruding tongue is present in 45% of children with DS. 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.

Many DS syndrome patients have a significant hearing loss, usually of the conductive type. Sight problems (44-71%) and cataracts are common in DS individuals of advanced age.

Obstructive sleep apnea is common in DS, and is increasingly being recognised as a cause of morbidity in this population. Prevalence is currently estimated between 54-90% (Simpson, Oyekan, Ehsan, & Ingram, 2018). Symptoms include loud snoring, heavy breathing, restless nights and daytime sleepiness, as well as neurocognitive symptoms such as irritability, depression, paranoia, cognitive decline and behavioral problems.

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

Epilepsy is present in 8% of children with DS, 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).

Duodenal stenosis/atresia, Hirschsprung disease and acute megakaryocytic leukemia occur 250-, 30- and 300-times more frequently, respectively, in patients with DS than in the general population. In addition, for any given phenotype there is considerable variability (severity) in expression. DS is also associated with an increased incidence of autoimmune disorders, such as autoimmune thyroiditis, primary sclerosing cholangitis, insulin dependent diabetes mellitus, celiac disease and alopecia areata (Alexander *et al.*, 2016; Bittles, Bower, Hussain, & Glasson, 2007; Glasson, Dye, & Bittles, 2014). People with DS are prone to disorders of the thyroid gland (15% develop hypothyroidism during childhood or adolescence).

People with DS have increased incidence of behavioural and mental health problems compared to the general population (Tassé *et al.*, 2016). Depressive and anxiety disorders appear to be more prevalent . A small subgroup of adolescents and young adults with DS are observed to undergo acute regression, which has also been termed Down Syndrome Disintegrative Disorder, with loss of skills and independence compared to their previous levels of functioning. At present the cause of this decline is unknown, although

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often the decline appears to occur after exposure to emotional stressors (Mircher *et al.*, 2017).

On the other hand, DS seems be protective against other conditions, such as multiple sclerosis, Crohn disease, neuroblastoma and the development of most solid tumors, which are rarely reported in association with DS.

Behavioural characteristics

DS is the most common genetic cause of intellectual disability with the majority of individuals with this syndrome classified in the mild – moderate range. Their cognitive profile demonstrates strengths in visual learning, but relative weaknesses in expressive language, verbal working memory, and episodic memory (Grieco, Pulsifer, Seligsohn, Skotko, & Schwartz, 2015). However, there is a wide range of cognitive function with variations in IQ, language, attention, memory and functional abilities (Karmiloff-Smith *et al.*, 2016)

Fewer behavior problems compared to controls with cognitive disability have been described in DS but are more frequent than in sibling or in controls with normal IQ. Children with DS may be at a lower risk for significant behavioral comorbidities in that they show a lower profile of maladaptive behaviors compared to children with other intellectual disabilities. However, in comparison to typically developing age-matched peers, children with DS show higher rates of inattention, oppositional behaviors, and impulsivity (Dykens, 2007).

People with DS 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 DS 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 over-represented, and many people with DS 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 adult DS subjects without dementia. This suggested a more positive pattern for ageing adults with DS until symptoms of dementia develop (Makary *et al.*, 2014).

Cognitive characteristics

Intellectual disability (ID) is present in almost all patients with DS, but with individual ability varying widely, from borderline to profound ID (Karmiloff-Smith *et al.*, 2016).

Most children and adults with DS function in the mild or moderate range, 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). Difficulties in syntax expression and comprehension are common throughout the lifespan, and verbal working memory is a noted weakness.

Visuo-spatial skills have historically been postited as a comparative strength for indivduals with DS, particularly in comparison to general verbal abilities and verbal memory, which is a particular weakness. However, by compiling results from multiple studies, a more nuanced picture is seen. While spatial sequential memory skills are in line with general abilities, individuals with DS may show specific difficulties in wayfinding and spatial working memory (Yang, Conners, & Merrill, 2014).

Deficits in attention and executive functioning are seen at all ages. Individuals with DS 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).

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

Alzheimer's disease and dementia

In adults with DS, neuropathological changes typical of Alzheimer's disease 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 DS (Hithersay *et al.*, 2018). On post-mortem examination, almost all adults with DS 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 DS 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 DS, earlier dementia onset is associated with earlier menopause (Coppus *et al.*, 2010).

While there is a clear association with APP and AD in DS (see above), non-chromosome 21 genes that are known to influence AD-onset in the non-DS populations, such at APOE, assert a similar influence in DS (Hithersay *et al.*, 2018; Lai *et al.*, 1999). Further, mouse-model 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 DS 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).

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

As dementia advances, neurological features become more apparent, with incontinence and Parkinsonian traits commonly seen (Strydom *et al.*, 2010). Late-onset seizures develop in more than 40% of individuals with DS 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).

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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. Targeted treatments have been developed to reverse 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 clinical problems and these individuals usually have a favorable activation ratio, meaning the majority of their cells have the normal X as the active X as measured in blood. The diagnosis of fragile X syndrome is made by FMR1 DNA testing. Cytogenetic studies may also show the fragile site in folate deficient media, but DNA studies are essential for diagnosis and to identify the CGG repeat expansion number. More recent whole genome and whole exome studies have documented point mutations and deletions in FMR1 that can lead to a fragile X syndrome phenotype without the CGG expansion because the FMRP is abnormal or partially deleted.

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

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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. 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 in the middle cerebellar peduncles, splenium, insula, pons and 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 with 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 normal life expectancy except for those who have seizures. 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

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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% 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 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. Arbaclofen, a GABAB 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 but a new trial in children ages 3 to 6 with AFQ056 combined with a parent implemented language intervention (PILI) through Skype is ongoing currently. A controlled trial of a low dose of sertraline (2.5 to 5.0 mg) in children ages 2 to 6yo demonstrated efficacy in developmental profiles and is often used clinically. Anecdotal cases have demonstrated a benefit from metformin treatment in language skills and behavior. Metformin has rescued the fragile X phenotype in animal models and it is now undergoing a controlled trial in children ages 6 to 25yo at multiple centers. A multicenter trial of a topical ointment with cannabidiol (CBD) is also undergoing a controlled trial at multiple centers to target anxiety. In addition, a new GABA agonist Gaboxidol is also undergoing studies of two dosage regimens. These studies will likely lead to many more

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treatment options for those with fragile X syndrome and some of the targeted treatments may improve language and cognition in this disorder.

Resources

- **The Fragile X Society**, 53 Winchelsea Lane, Hastings, East Sussex, TN35 4LG. 01424 813 147
- **The National Fragile X Foundation**, P.O. Box 37, Walnut Creek, California, 94597, USA. 800 – 688 – 8765
- **FRAXA Research Foundation**, 45 Pleasant St., Newburyport, MA 01950, USA. 978 – 462 – 1866

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Randi Hagerman MD, August 2015
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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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15. CMS standard: 482.13. (e) (6).) Exception: "Repetitive self-mutilating behavior. If a patient is diagnosed with a chronic medical or psychiatric condition, such as Lesch-Nyhan Syndrome, and the patient engages in repetitive self-mutilating behavior, a standing or PRN order for restraint to be applied in accordance with specific parameters established in the treatment plan would be permitted. Since the use of restraints to prevent self-injury is needed for these types of rare, severe, medical and psychiatric conditions, the specific requirements (1-hour face-to-face evaluation, time-limited orders, and evaluation every 24 hours before renewal of the order) for the management of violent or self- destructive behavior do not apply."
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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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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

RTS is a multiple congenital anomaly syndrome. The first genetic abnormalities identified were breakpoints, mutations and microdeletions within chromosome 16p13.3. Molecular analysis subsequently highlighted a gene located on chromosome 16p13.3 that coded for the cyclic AMP response element binding protein (CBP). In addition to the chromosomal rearrangements of chromosome 16, RTS can also arise from heterozygous point mutations in the CBP gene itself. More recently, the E1A Binding Protein, P300 has also been implicated. P300 is located at 22q13.2 and is a homolog of CBP. Both are highly related in structure and function and consequently mutations in p300 can also result RTS. There are only a small number of clinical reports of RTS caused by mutations in p300 and these reports have indicated individuals are often more mildly affected, particularly in terms of the skeletal features and degree of intellectual disability. However, in some cases, comparisons between those with a p300 mutation and those where the CBP gene is implicated are identical. Genetic markers are found in around 65-70% of cases and therefore some individuals are diagnosed through clinical characteristics.

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. The classical facial appearance in RTS is also well documented. Descriptions typically include a prominent 'beaked' nose, eyes with downward slanting palpebral fissures, long eyelashes, thick eyebrows, and a small mouth. Feeding and related weight difficulties have been reported in the literature, 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. Importantly, it has been documented that individuals with RTS may suffer an increased risk of developing cancer. Therefore, attention to early symptoms indicative of tumours is important to ensure early intervention.

Behavioural characteristics

Although still in its infancy, the literature outlining the behavioural phenotype of RTS is growing. Studies have described "stubbornness", sleeping difficulties and a tendency for individuals to be "emotional" and "excitable". The presence of ADHD-type behaviours such as impulsivity and hyperactivity has also been noted. The two most frequently noted characteristics relate to social behaviour and repetitive behaviour. 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. 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 superior social competency and social communication skills when compared to those with other causes of ID. In a recent study comparing children with RTS to a matched heterogeneous intellectual disability (HID) group, findings showed that those with RTS showed superior performance on items including acceptance

of physical contact, initiating play with other children, and quality of eye contact. In this same study individuals with RTS displayed significantly higher scores than matched HID controls on items assessing the stereotypies 'flaps arms/hands when excited', 'extremely pleased with certain movements/keeps doing them' and 'makes odd/fast movements with fingers/hands'. In a recent study, individuals with RTS were more likely to experience heightened levels of anxiety in comparison to typically developing children. It has also been suggested that individuals with RTS may be at increased risk of mood instability, as they get older, such as anxiety and depression. However, more evidence is needed to corroborate this finding.

Cognitive characteristics

Intellectual disability (ID) is an associated characteristic of RTS. Although estimates regarding the degree of ID have varied across studies it is thought that most individuals lie within the mild to 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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Laurie Powis, Jane Waite and Chris Oliver, August, 2014
Georgina Edwards, Laurie Powis, Jane Waite and Chris Oliver (updated March 2019)

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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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Triple-X syndrome (47,XXX)

First description and alternative names

In 1959 Jacobs (Jacobs *et al.* 1959) first described triple-X syndrome in an infertile patient. The term "super female" is considered to be 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. The triple-X 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 en Edinburgh) published follow-up data in young adults (Otter *et al.* 2010). The most recent studies, from other research groups, published data from more or less biased groups of cases (Wilson *et al.* 2019).

Genetics and molecular biology

In triple-X syndrome 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.

In 46,XX females the extra X chromosome is silenced through lionization. The extra X chromosome in triple-X women is also silenced. In 46,XX females one-third of the genes on the X chromosome escape silencing (Migeon 2007). The so-called 'late-replicating' X chromosome is the second X chromosome. In cases of an extra X chromosome there is another late-replicating chromosome, so replication time increases during each cell division (Barlow 1973). The extra X chromosome might also have some influence on the nuclear architecture and on epigenetic processes (Kelkar and Deobagkar 2010, Jowhar *et al.* 2018).

Whether incomplete silencing of the extra X chromosome, the prolonged cell cycle during division and/or epigenetic phenomena are relevant during development in 47,XXX, requires further research (Katsir & Linial 2019) .

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 triple-X syndrome. 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; there seems to be a relationship between head circumference and the level of cognitive functioning (Ratcliffe *et al.* 1994). Motor and coordination abilities seem to be somewhat retarded, and the girls are sometimes described as being clumsy. Neuroimaging studies revealed a smaller head circumference and a lower brain volume (Patwardhan *et al.* 2002).

Since 1959 many physical disorders associated with a triple-X finding 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 triple-X cases: urogenital anomalies, (partial) epilepsy and Premature Ovarian Failure (POF) and infertility (Tartaglia *et al.* 2010, Stochholm *et al.* 2010).

Behavioral and psychiatric characteristics

Low self-esteem seems to be the most common feature (Otter *et al.* 2010, Freilinger *et al.* 2018). Social anxiety/shyness and executive dysfunction are common in triple X girls (van Rijn *et al.* 2013, van Rijn and Swaab 2015, Lenroot *et al.* 2014). Social cognitive problems are common in triple X girls, probably due to language disorders (Bishop *et al.* 2011, Wilson *et al.* 2019). Another study in triple X girls showed a developmental pattern that resembled the development of girls with autism with mild or late presenting autism symptoms (van Rijn *et al.* 2014). Challenging behaviour may be the result of any of these developmental difficulties. Triple X girls living in

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a stable family function better than triple-X girls in an unstable family (Netley 1986). The triple X 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).

There seems to be a higher prevalence of psychiatric illness in general, especially in (mildly) mentally retarded cases, although we should be careful for there is still a paucity of data on development in adults. More specifically, it concerns a higher prevalence of psychotic disorders and adjustment disorders (Olanders 1975). The newborn-screening studies were stopped before the age that psychotic disorders could have become noticeable. Further psychiatric research with standardised psychiatric diagnostic tools is warranted in these females. Adults seem to face physical, social and occupational problems (Otter *et al.* 2012, Stochholm *et al.* 2010, Stochholm *et al.* 2013).

A study from Germany demonstrated that the extra X chromosome may influence mental health and well being into adulthood. This study made clear, again, that many women with an extra X chromosome do not experience major problems (Freilinger *et al.* 2018)

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 and 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 neuroiamaging in individual cases.

Neuropsychological characteristics

Data on intelligence in girls and adolescents are consistent, indicating that the full-scale IQ's are almost 20 points lower than what would be 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 quite common (Robinson *et al.* 1990, Bishop *et al.* 2011). Further research is needed to confirm the findings on increased prevalence of attention problems and to explain these attention problems: are they due to receptive language disorder, auditory processing disorders or attention deficit disorder (ADD) (Lenroot *et al.* 2014)? Clinical experience in 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).

Available guidelines for behavioral 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 sincere advice to use a broad set of tools during this assessment, since recent studies indicate language imparments (Bishop *et al.* 2018, van Elst *et al.* 2020), social behavioural problems (Wilson *et al.* 2019) and neurocognitive problems, executive dysfunction among others (Urbanus *et al.* 2020).

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 triple-X 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 and https://www.rarechromo.org/media/information/Reports/XXX%20Study%20Day%20Report%20FTNW.pdf

- The AXYS website provides a lot of information: https://genetic.org/variations/about-trisomy-x/. Especially parents and triple-X girls/women in the United States will find opportunities to meet experts, other parents and triple-X girls/women. KS&A is active in fundraising for the support of scientific research..

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Dr. Maarten Otter, Psychiatrist, Spring 2015

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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 (Northrup, Krueger *et al.*, 2013). Mutations are identified in >90% of individuals with clinically confirmed TSC.

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 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 a summary term for all the bio-psycho-social aspects of the disorder (Krueger *et al.*, 2013; 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). 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

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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).
- 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.
- 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.
- The diagnostic criteria and management guidelines for TSC were revised in 2012 and were published in 2013 (Northrup, Krueger *et al.*, 2013; Krueger, Northrup *et al.*, 2013).

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]

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Petrus J de Vries, (updated July 2015)
Petrus J de Vries & Anna Jansen (updated July 2019)

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

- Bondy C.A. (2007) *Turner Syndrome Study Group. Care of girls and women with Turner syndrome: A guideline of the Turner Syndrome Study Group.* J Clin Endocrinol Metab 92(1), 10 – 25.

- 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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Updated: David H Skuse & Jeanne Wolstencroft, March 2021
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 and conotruncal anomaly face syndrome.

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 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 3,000 to 1 in 6,000 live births [e.g., 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]. 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 [12]. It is also likely that the prevalence of the syndrome will rise as mortality decreases and reproductive fitness increases [13, 14]. The syndrome affects individuals of both sexes and of different ethnic background equally [15] although it has been suggested that there are sex differences in the expression of the syndrome [e.g., 16, 17].

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 [18]. The most common features include congenital heart defects (including conotruncal anomalies), palatal anomalies (including submucous cleft palate and/or velopharyngeal incompetence); immunodeficiency; hypocalcaemia and subtle facial characteristics [9] .

Behavioural characteristics

High levels of internalising symptoms and poor social skills are common amongst children with the syndrome [19]. Children with 22q11.2DS are also at higher risk of developing psychiatric disorders such as attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder, anxiety disorders (generalised anxiety disorder, separation anxiety, and phobias) and, arguably autism spectrum disorders [20]. In late teenage years and early adulthood there are an increased risk of depressive disorders and also a high risk of psychotic disorders including schizophrenia. 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 (Young *et al.*2011; Tang *et al.*2014).

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, numeracy, 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 [e.g., 25, 26, 27]

Available guidelines for behavioural assessment/ treatment/management

- Practical guidelines for managing adults with 22q11.2 deletion syndrome [28]
- Practical guidelines for managing patients with 22q11.2 deletion syndrome [12]
- Towards a safety net for management of 22q11.2 deletion syndrome: guidelines for our times [29]
- Consensus Document on 22q11 Deletion Syndrome (22q11DS), MaxAppeal http://www.maxappeal.org.uk/downloads/Consensus_Document_on_22q11_Deletion_Syndrome.pdf

Useful websites/associations for more information

- International 22q11.2 Foundation http://www.22q.org/
- 22q11.2 Society http://www.22qsociety.org/

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Linda Campbell : June 2016

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

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.

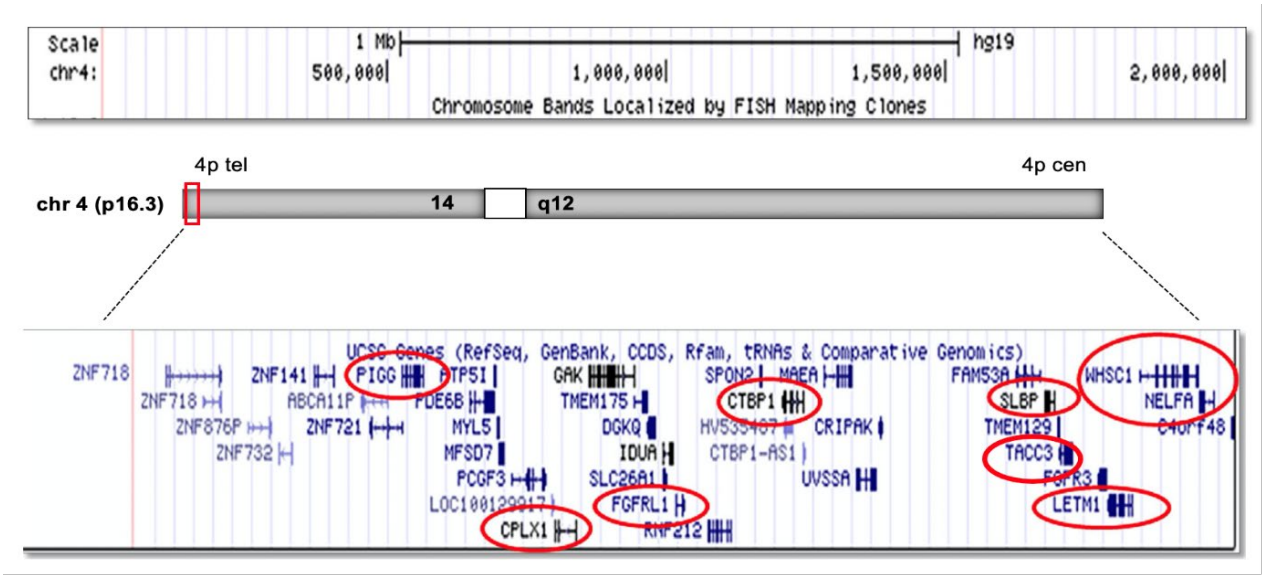

Figure 1. Diagram showing the distal region of chromosome 4p, where candidate genes for seizures and craniofacial features map (LEMT1 and WHSC1; Zollino *et al.*, 2003; Rodrıguez *et al.*, 2005). [Diagram was modified from Battaglia *et al.*, 2015].

Genetics and Molecular Biology

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, Figure 2).

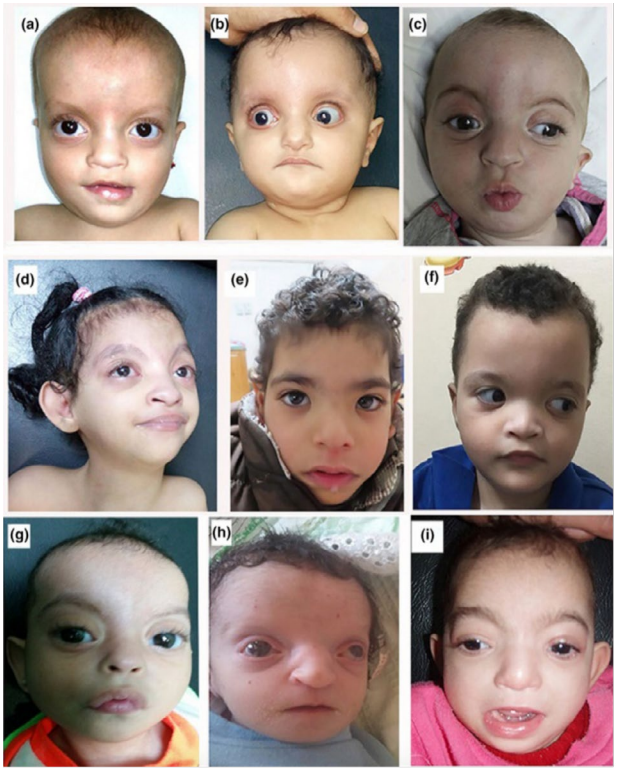

Figure 2: Typical facial features including the Greek warrior helmet, frontal bossing, sparse scalp hair, low set ears, broad nasal bridge, hypertelorism, epicanthic folds, high forehead, proptosis and ectropion, indicative of WSH syndrome. Ptosis in pt. no. 8, 9 and 10; squint in pt. no. 7 and 9; upward eyelid slanting in pt. no. 1, 2, 5, 8 and 10; downward eyelid slanting in pt. no. 3, 6, 7 and 9 [Mekkawy *et al.* 2020]

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

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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

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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

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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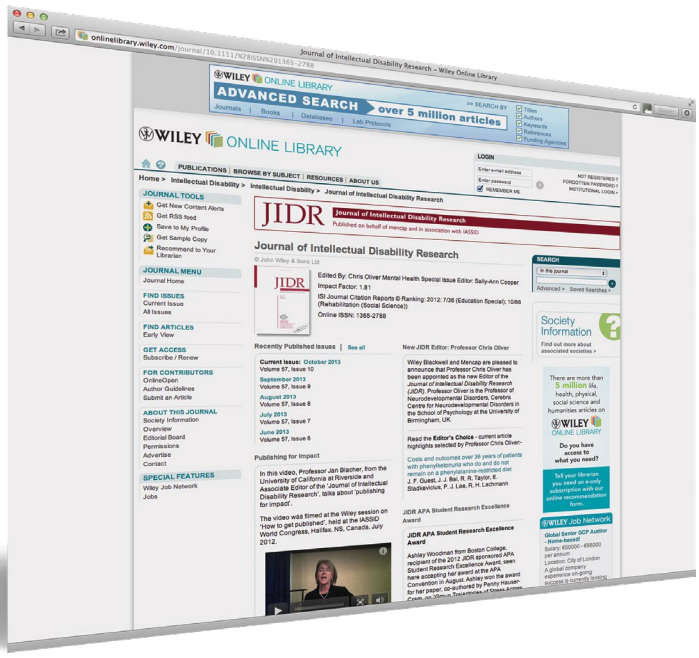

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