23rd SSBP International Research Symposium

Programme Book

9th – 10th September 2021 • Virtual Symposium

Save the date!

24th SSBP International Research Symposium will be held in Oslo, Norway 8th–10th September 2022

Abstract submission opens: 1st April 2022
Registration opens: 1st May 2022
Deadline for online abstract submission: 20th May 2022
Deadline for discounted early bird registration: 31st July 2022

Educational Day: 8th September 2022
Research Symposium: 9th–10th September 2022

Join us in Oslo, Norway for our 24th Research symposium, the theme will be *Developmental disorders and behavioural phenotypes across the lifespan*

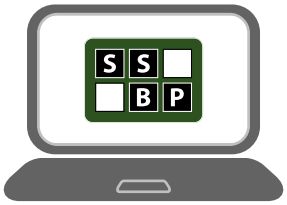
See **www.ssbp.org.uk** for further information
and details on how to submit an abstract for an oral or poster presentation

The Society for the Study
of Behavioural Phenotypes

9th– 10th September 2021

The 23rd SSBP International Research Symposium

Virtual Symposium



www.ssbp.org.uk

Zoom

Gather

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Welcome from the Conference Organisers

We are delighted to welcome you to the 23rd Society for the Study of Behavioural Phenotypes International Research Symposium, and this year we are virtually welcoming people from all corners of the world including Africa, India, Australia, UK, Europe and the United States of America.

The current pandemic has been challenging for many of us, with changes to the way we live and work, and for many, friends and family who have been unwell. Our thoughts are with members of the Society who have faced these challenges this year. We had felt it was too risky to hold a face to face meeting so we postponed the planned meeting in Oslo to 2022 and elected to meet 'face to face' in a virtual world.

It is with many thanks to Becky Windram, and with Damian MacNamara's invaluable website support, that we as the organising committee have put together what we believe is a great Research symposium. We have attempted to make at least some of the conference live at a reasonable hour in all time zones - however recognising that this isn't possible for all, we will also make the presentations and posters available for 30 days after the meeting for those that have registered.

I am really excited about the program and the opportunities an online forum can offer particularly in accessibility for our colleagues from low and middle income countries and I am particularly excited to say that this year we have had our greatest number of registrants from these countries so would like to offer them a special welcome to this 23rd Research symposium. This year in lieu of an Educational Day we will be hosting a series of Webinars during the year, for our junior members in particular, so for those that are interested please join the ECR student session at the end of session 3.

Our program has a mixture of themes based around our 6 exciting international keynote speakers: **Liz Pellicano** who will speak about her research involving autistic children, young people and adults; **Jonathan Green** speaking about developmental science and treatment innovations; **Allyson Berent** recounting a journey through drug development from parent to industry for Angelman syndrome; **Marjorie Solomon** discussing intellectual ability based phenotypes in autism spectrum disorders from childhood to preadolescence; **André Strydom** speaking about comorbidities associated with Down Syndrome; and **Elizabeth Berry-Kravis** discussing targeted treatments for Fragile-X syndrome. This is interspersed with free papers on a wide range of topics. Please take the time to see the presentations and do login for the live Q & As as well as the round tables, two live poster sessions and social sessions.

We hope you enjoy our 23rd International Research Symposium!

Honey Heussler, Pat Howlin and Flora Tassone
Conference Coordinators

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Virtual Conference Organisers

Associate Professor Honey Heussler

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

Professor Pat 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 Flora Tassone

Dr. Flora Tassone, Ph.D., is a Professor in the Department of Biochemistry and Molecular Medicine, and a MIND Institute Investigator at the University of California, Davis, School of Medicine. She has had a long-standing focus on the molecular mechanisms related to the FMR1-associated disorders, and is also actively involved in developing molecular biomarkers for predicting efficacy in target treatments for FXS and neurodevelopmental disorders. Dr. Tassone has extensive experience in medical genetics and clinical analysis. She has been granted multiple awards, fellowships and training opportunities, as well as research awards from NICHD, NIH, the National Fragile X Foundation, and UC Davis Health Systems for her outstanding contributions to the field

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Scientific Committee

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

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

Professor Flora Tassone
Professor, Dept. Biochemistry and Molecular Medicine,
MIND Institute Investigator

Dr Kristin Bakke
Senior Consultant,
NevSom, Dept. of Rare Disorders & Disabilities, Oslo University Hospital, Norway

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

Forthcoming Meetings of the SSBP

2022	Oslo, Norway	24th International

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The SSBP Executive Committee

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

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

Committee: International Representatives

Africa	*Petrus* ***de Vries*** (Cape Town) – petrus.devries@uct.ac.za
Australia	*Stewart* ***Einfeld*** (Camperdown) – s.einfeld@usyd.edu.au
Europe	*Kristin* ***Bakke*** (Oslo) – kristinb@ous-hf.no
USA (West Coast)	*Randi* ***Hagerman*** (Sacramento) – randi.hagerman@ucdmc.ucdavis.edu
Global	*Pat* ***Howlin*** (London) – patricia.howlin@kcl.ac.uk

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

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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

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

2021 Tom Oppé Distinguished Lecturer: Professor Liz Pellicano

Liz Pellicano is an Australian Research Council Future Fellow and Professor at Macquarie University, having previously been Professor of Autism Education and Director of the Centre for Research in Autism and Education at University College London.

She trained as a developmental cognitive psychologist at the University of Western Australia, where she also completed a PhD on the cognitive profile of autistic children in 2005, before becoming a Junior Research Fellow in Psychiatry at the University of Oxford, and Lecturer in Experimental Psychology at the University of Bristol.

Best known for her theoretical accounts of autistic cognition and perception, her current research seeks to identify ways to bridge the gap between lab and life and open up scientific investigation to greater involvement of autistic people themselves, with the aim of generating discoveries that bring real benefits to autistic people and their families.

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Patricia Howlin and the Patricia Howlin Prize Lecture

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

Pat Howlin Prize Lecture:

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

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

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

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

The award winner will receive free registration for the current SSBP Research Symposium along with a prize of £100 (or equivalent) and an award certificate - both of which will be presented to the winner during the SSBP Research symposium.

Patricia Howlin Lecturers

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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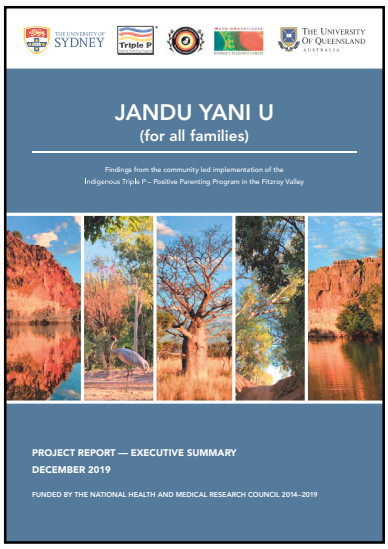
2021 Pat Howlin Lecturer: Stewart Einfeld and the Jandu Yani U research group

There were no suitable submissions from early career researchers in 2021.

The decision was taken to award the 2021 Pat Howlin Lecture to **Jandu Yani U research group** in recognition of the importance of this intervention focused project.

Stewart Einfeld will present the lecture on behalf of the team, and the Pat Howlin Prize money will go towards the project.



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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 will be launched at the 2019 SSBP conference, with a winner selected from among the abstracts submitted. Future abstract submission forms will 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 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 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

2019	Ms Siobhan Blackwell

2021 Leclezio-de Vries Lecture

Unfortunately, this year there were no abstracts entered for the Leclezio-de Vries Lecture in 2021 that fully met criteria for this award.

The SSBP would like to encourage researchers whose work focuses on community participation to consider submission for 2022.

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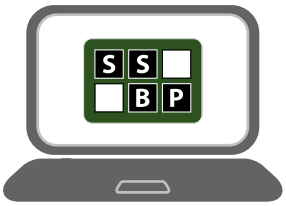
E-Venues

SSBP Website
www.ssbp.org.uk



The SSBP Website is the central base for the conference.

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

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

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

Zoom
zoom.us

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

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

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

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

Asking Questions

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

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

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

Gather
www.gather.town

The two Live Poster Sessions and social events will be hosted on Gather.

How to access:
Link: https://gather.town/invite?token=dTkZJrBi
Password: SSBP2021
Guide: https://ssbp.org.uk/wp-content/uploads/2021/09/SSBP-Guide-to-Gather.pdf

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

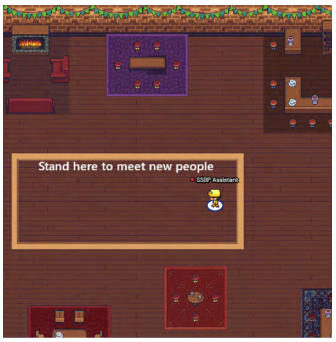
Poster authors will be available to discuss their posters in one of the two live poster sessions, depending on their timezone.

Gather will be open all day throughout the conference, so please do feel free to use the space as a place to drop in, and to meet and chat. (Make sure you take some time to discover the beach and gardens, and to relax in the virtual bar!)

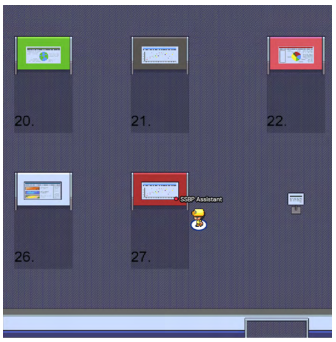
Gather is simple to use, but does take a few minutes to set up the first time you use it. We recommend that you follow **the SSBP Gather Guide, and either test out Gather before the first session, or allow an extra 10 minutes to get started.**

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

Main Hall



Bar



Poster Room

Beach

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Keynote Speaker Profiles:

(in order of presentation)

Professor Jonathan Green

Jonathan Green is Professor of Child & Adolescent Psychiatry in the University of Manchester, UK, and Honorary Consultant Child & Adolescent Psychiatrist at the Royal Manchester Children's Hospital. He studied medicine at Cambridge, Paediatrics in London and Psychiatry in Oxford before establishing work in Manchester with a clinical and research focus on early social developmental science and early intervention in autism.

He has led RCTs of the Paediatric Autism Communication Therapy (PACT) and iBASIS prodromal infancy interventions, showing sustained effects on symptom severity; plus PACT adaptation for low and medium income country contexts using task-shifting to non-specialists (PASS and PASSPLUS). He also investigates adjunctive biological treatments within monogenic syndromic models of autism such as Neurofibromatosis 1, within basic science collaborations and experimental trials. Clinically, he runs the Social Development Clinic at the Royal Manchester Children's Hospital, undertaking assessment and treatment innovation with ASD and other impairments of social development.

Jonathan has been associate editor for JCPP, a member of the NICE guideline group for autism treatments and a MRC collaboration into causal analysis in clinical trials. He is the International Society for Autism Research Global Senior Leader for the UK and an NIHR Senior Investigator.

http://research.bmh.manchester.ac.uk/socialdevelopment/

Dr Allyson Berent

Dr. Allyson Berent is a veterinary internal medicine specialist who serves as the Director of Interventional Endoscopy Services at the largest animal hospital in the world, The Animal Medical Center, in New York City. After graduating from Cornell University College of Veterinary Medicine she completed an internship at the University of Minnesota and a residency in Small Animal Internal Medicine at the Veterinary Hospital of the University of Pennsylvania. After completing a fellowship in interventional radiology at the Veterinary Hospital of the University of Pennsylvania, a fellowship in Endourology at Thomas Jefferson University, and an Interventional radiology fellowship at the Hospital of the University of Pennsylvania, she served as an Adjunct Assistant Professor in Internal Medicine and Interventional Radiology/ Interventional Endoscopy at the Matthew J. Ryan Veterinary Hospital of the University of Pennsylvania. Dr. Berent has a particular focus on medical device development, stem cell therapy through regenerative medicine and selective arterial delivery, ureteral diseases, urinary incontinence and minimally invasive management of upper tract urinary obstructions and biliary obstructions.

In 2014 Dr. Berent's daughter was diagnosed with a rare non-degenerative neurogenetic disorder called Angelman syndrome. In October of 2015 she joined to Board of Directors as a Scientific Director for the Foundation for Angelman Syndrome Therapeutics (FAST), and in March of 2016 became the Chief Science Officer for the Foundation. Dr. Berent helped to spearhead the development of a pre-competitive biomarker and outcome measure consortium in order to bring patient focused outcome measures forward for human

clinical trials (Angelman Syndrome Biomarker and Outcome Measure Consortium-ABOM) and Co-Founded the International Angelman Syndrome Research Council (INSYNC). Through FAST, Dr. Berent collaborated with a consortium of scientists to encourage translational research opportunities, in order to help bring novel genetic therapies forward toward human clinical trials. Through this work, with the foundation, Dr. Berent co-founded GeneTx Biotherapeutics, a company singularly focused to advance an antisense oligonucleotide (ASO) therapy through IND enabling studies and a phase 1/2 clinical trial. Dr. Berent currently serves as the Chief Operating Officer of GeneTx Biotherapeutics, who partnered with Ultragenyx Pharmaceuticals in August of 2019. The Phase 1/2 clinical trial started enrolling patients in February 2020 as the first intrathecally delivered ASO for Angelman syndrome, a study of safety and tolerability of GTX-102.

Professor Marjorie Solomon

Dr. Marjorie Solomon is a Professor of Psychiatry at the Department of Psychiatry and Behavioral Sciences at the University of California-Davis, Associate Director of the MIND Institute, and Associate Director of the Imaging Research Center. Dr. Solomon's laboratory studies cognitive development in autistic children, adolescents, and young adults. Her work utilizes neuropsychological and cognitive neuroscience methods including fMRI.

At SSBP, Dr. Solomon will present an overview of her work in the Autism Phenome Project longitudinal cohort that highlights the development of the intellectual ability level trajectories from early childhood through adolescence and the distal correlates of these trajectories related to adaptive communication and autism symptoms. This work is critical given that IQ is the strongest predictor of outcomes in individuals with autism and typical development, and that it constitutes the most significant source of heterogeneity within the ASD phenotype.

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Professor André Strydom

Dr André Strydom (MRCPsych, MSc, PhD) is a Professor in Intellectual Disabilities at the Institute of Psychiatry, Psychology and Neuroscience at King's College London, where his research is focused on mental disorders in adults with neurodevelopmental conditions, including Down syndrome and other genetic disorders.

Professor Strydom is particularly interested in ageing-related conditions such as dementia in adults with Intellectual Disability and Down syndrome. He was the chief investigator of the LonDownS consortium, a collaboration on various aspects of Alzheimer's disease in Down syndrome. One of the important aims of ongoing work is to deliver the knowledge, tools and expertise that is necessary to enable clinical trials of treatment to prevent or delay the onset of dementia in individuals with Down syndrome.

He leads a partnership funded by NHSE's National Learning disability and Autism programme to analyse data from LeDeR reviews of hospital deaths, and to identify quality improvements and better treatments to reduce health inequalities and premature mortality. He also directs KCL's Nerodevelopmental disorders clinical trials centre which hosts RCTs of medication treatments to reduce morbidity associated with intellectual disabilities and autism.

Professor Strydom works as a Consultant Psychiatrist in Intellectual Disabilities at the South London and the Maudsley NHS Foundation Trust.
@drandrestrydom

Professor Elizabeth Berry-Kravis

Elizabeth Berry-Kravis MD, PhD is a Professor of Pediatrics, Neurological Sciences, and Biochemistry at Rush University Medical Center in Chicago. She established the Fragile X Clinic and Research Program in 1991, through which she provides care to over 700 patients with fragile X syndrome (FXS). She has studied medical issues, epilepsy and psychopharmacology in FXS, and has been a leader in translational research in FXS including development of outcome measures and biomarkers, natural history studies, newborn screening, and particularly clinical trials of new targeted treatments in FXS, and her laboratory studies the cellular role of fragile X mental retardation protein (FMRP), relationship between FMRP and clinical function, and optimization of genetic testing methods. More recently she has expanded clinical and translational work to other neurodevelopmental disorders and genetic neurodegenerative diseases including autism spectrum disorders, Phelan McDermid syndrome, Rett syndrome, Angelman syndrome, Niemann-Pick type C, Battens disease, pantothenate kinase-associated neurodegeneration, and creatine transporter deficiency. She has received the NFXF Jarrett Cole Clinical Award, FRAXA Champion Award, NFXF William and Enid Rosen Research Award, March of Dimes Jonas Salk Research Award, American Academy of Neurology Sidney Carter Award in Child Neurology and John Merck Fund Sparkplug Award.

Research Symposium Programme

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

Session 1 – Thursday 9th September 2021

Time (UK BST)		Session 1	E- venue
08:00 – 08:30		**KEYNOTE – THE TOM OPPÉ DISTINGUISHED LECTURE:** 1. **Liz Pellicano** – Reimagining Autistic Education: Lessons Learnt From Remote Learning During Lockdown	*Website*
08:30 – 09:00		**Free Communications** *(3 x 10 min)*	*Website*
		2. **Claudine Kraan** – Wearable digital gait-based outcome measures for children with Fragile X, Prader-Willi and Angelman syndromes	
		3. **Stacey Bissell** – Sleep and behaviour in children with tuberous sclerosis complex: A remote study using actigraphy and mobile app technology	
		4. **Stephanie Vanclooster** – The research landscape of Tuberous Sclerosis Complex-Associated Neuropsychiatric Disorders (TAND) – A comprehensive scoping review	
09:05 – 09:35	**LIVE**	**Welcome to the Conference**	*Zoom*
		Q/A Discussion (Chair: Anna Jansen) – *Pellicano, Kraan, Bissell, Vanclooster*	
09:35 – 09:45		**BREAK** *(10 min)*	
09:45 – 10:15		**KEYNOTE:** 5. **Jonathan Green** – Developmental Science and Treatment Innovation	*Website*
10:15 – 10:45		**Free Communications** *(3 x 10 min)*	*Website*
		6. **Charlotte Tye** – Atypical visual attention predicts emerging autistic traits in infants with tuberous sclerosis complex	
		7. **Helen Heussler** – Longer Term Tolerability and Efficacy of ZYN002 Cannabidiol Transdermal Gel in Children and Adolescents with Autism Spectrum Disorder (ASD): An Open-Label Phase 2 Study (BRIGHT [ZYN2-CL-030]}	
		8. **Natalie Bozhilova** – Autism-related phenotypes in genetic syndromes	
10:50 – 11:15	**LIVE**	**Q/A Discussion** (Chair: Petrus de Vries) – *Green, Tye, Heussler, Bozhilova*	*Zoom*
11:15 – 11:30		**BREAK** *(15 min)*	
11:30 – 12:00	**LIVE**	**A tribute** in memory of **James Harris**, a longstanding member of the SSBP. Followed by:	*Zoom*
		Round Table discussion (Chair: Kate Woodcock) – *Panel: Vanessa Sarkozy, Andrew Stanfield, Agnies van Eeghen, Jeanne Wolstencroft*) – Challenges in evaluating and implementing interventions for aspects of behavioural phenotypes	
12:00 onwards		**Post-session Social event** – Virtual Coffee / Bar	*Gather*

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Session 2 – Thursday 9th September 2021 (Friday 10th September AUS)

Time (UK BST)		Session 2	E- venue
17:00 – 17:30		**KEYNOTE: 9. Allyson Berent** – From Impossible to Possible: A Personal Journey From Diagnosis Through Drug Development for Angelman Syndrome.	*Website*
17:30 – 18:10		**Free Communications** *(4 x 10 min)*	*Website*
		10. Donna McDonald-McGinn – Genes to Mental Health Network Report: Stakeholders Perspectives on Research Participation	
		11. Maria Cristina Teixeira – Parental perception of emotional/behavioural problems in Brazilian children and adolescents with Williams syndrome	
		12. Charlotte Willfors – Williams syndrome: On the role of intellectual abilities in anxiety	
		13. Doesjka A. Hagenaar – Child characteristics associated with parental stress and child/parental quality of life in Angelman syndrome	
18:20 – 18:50	**LIVE**	**Welcome from the Organisers**	*Zoom*
		Q/A Discussion (Chair: Flora Tassone) – *Berent, McDonald-McGinn, Teixeira, Willfors, Hagenaar*	
18:50 – 19:00		**BREAK** *(10 min)*	
19:00 – 19:30		**KEYNOTE: 14. Marjorie Solomon** – Intellectual Ability Based Phenotypes in Autism Spectrum Disorders From Early Childhood to Preadolescence.	*Website*
19:30 – 20:00		**Free Communications** *(3 x 10 min)*	*Website*
		15. Carole Samango-Sprouse – The Effect of Early Hormonal Treatment (EHT) on Neuromotor Capabilities in Infants and Toddlers with 47,XXY	
		16. Sophia Song – Incidence of Mental Health Disorders and Behavioural Complications in a Large Cohort of Teenagers with 47,XXY (Klinefelter Syndrome)	
		17. Nicole Tartaglia – The eXtraordinarY Babies Study: Early Developmental and Adaptive Functioning Profiles of Infants and Toddlers with Prenatally Identified Sex Chromosome Trisomies	
20:00 – 20:30	**LIVE**	**Q/A Discussion** (Chair: Pat Howlin) – *Solomon, Samango-Sprouse, Song, Tartaglia*	*Zoom*
20:30 – 20:45		**BREAK** *(15 min)*	
20:45 – 21:15	**LIVE**	**Live Poster Session A** – Poster authors from North and South America, Europe, Africa	*Gather*
21:15 onwards		**Post-session Social event** – Virtual Coffee / Bar	*Gather*

Session 3 – Friday 10th September 2021

Time (UK BST)		Session 3	E- venue
08:00 – 08:30	**LIVE**	**Live Poster Session B** – Poster authors from Europe, Africa, Asia, Australasia	*Gather*
08.30 – 08.45		**BREAK** *(15 min)*	
08:45 – 09:15		**KEYNOTE: THE PAT HOWLIN LECTURE:** **18. Stewart Einfeld** – An intervention to support families affected by Fetal Alcohol Spectrum Disorder (FASD) in a remote Australian Indigenous community	*Website*
09:15 – 09:45		**Free Communications** *(3 x 10 min)*	*Website*
		19. Archisman Mazumder – The Relationship Between Sensory Sensitivity and Maladaptive Behaviours in Children with Cornelia de Lange Syndrome	
		20. Evelien Urbanus – The behavioural profile of children with sex chromosome trisomy: Neurocognitive underpinnings of behavioural outcomes	
		21. Hanna Björlin Avdic – Neurodevelopmental and Psychiatric Disorders in females with Turner Syndrome: A Population-Based Study	
09:45 – 10:15	**LIVE**	**Q/A Discussion** (Chair: Pat Howlin) – *Einfeld, Mazumder, Urbanus, Björlin Avdic*	*Zoom*
10:15 – 10:30		**BREAK** *(15 min)*	
10:30 – 11:00		**KEYNOTE: 22. André Strydom** – Comorbidities Associated with Down Syndrome Across the Lifespan	*Website*
11:00 – 11:30		**Free Communications** *(3 x 10 min)*	*Website*
		23. Jente Verbesselt – Cross-sectional and longitudinal characterization of the developmental phenotype in 22q11.2 duplication	
		24. Jeanne Wolstencroft – Inheritance matters: Mental health risk in intellectual disability	
		25. Sarah Charles – The effect of the initial UK COVID-19 lockdown on the mental health of families with and without a child with a rare disorder	
11:35 – 12:00	**LIVE**	**Q/A Discussion** (Chair: Jane Waite) – *Strydom, Verbesselt, Wolstencroft, Charles*	*Zoom*
12:00 – 13:00	**LIVE**	**ECR / Student Webinar – Navigating Research Post-PhD** (Chair: Laura Roche) **All students and Early-Career Researchers Welcome**	*Zoom*

Session 4 – Friday 10th September 2021 (Saturday 11th September AUS)

Time (UK BST)		Session 4	E- venue
17:00 – 18:00		**Free Communications** *(6 x 10 min)*	*Website*
		26. Deborah Fidler – Latent Profiles of Autism Symptoms in Children and Adolescents with Down Syndrome	
		27. Kyra Lubbers – Autism symptoms in children and adolescents with Fragile X, Angelman Syndrome, Tuberous Sclerosis Complex and Neurofibromatosis Type 1: a cross-syndrome comparison	
		28. Joanne Tarver – Behavioural and Emotional Characteristics in Children with Bardet-Biedl Syndrome: A Cross Group Comparison	
		29. Somer Bishop – Use of language-based routing items to improve parent-report measures of social communication	
		30. Elaine Tierney – Sterol and lipid analyses identifies hypolipidemia and apolipoprotein disorders in autism associated with adaptive functioning deficits	
		31. Cathelijne Linders – Genotype differences in Smith-Magenis syndrome	
18:05 – 18:30	**LIVE**	**Q/A Discussion** (Chair: Jane Waite) – *Fidler, Lubbers, Tarver, Bishop, Tierney, Linders*	*Zoom*
18:30 – 18:45		**BREAK** *(15 min)*	
18:45 – 19:15		**KEYNOTE: 32. Elizabeth Berry-Kravis** – Targeted Treatments for Fragile X Syndrome: Lessons and Progress	*Website*
19:15 – 19:45		**Free Communications** *(3 x 10 min)*	*Website*
		33. Flora Tassone – Global Methylation Profiling in Children with Autism Spectrum Disorder and in Children with Fragile X Syndrome	
		34. Marwa Zafarullah – Metabolomic Biomarkers are Associated with Area of the Pons in Fragile X Premutation Carriers at Risk for Developing FXTAS	
		35. Randi Hagerman – A Pivotal Study of ZYN002 Cannabidiol (CBD) Transdermal Gel in Children and Adolescents With Fragile X Syndrome [CONNECT-FX (ZYN2-CL-016)]	
19:50 – 20:15	**LIVE**	**Q/A Discussion** (Chair: Kristin Andersen Bakke) – *Berry-Kravis, Tassone, Zafarullah, Hagerman*	*Zoom*
20:15 – 20:30		**BREAK** *(15 min)*	
20:30 – 20:55	**LIVE**	**Round Table discussion** (Chair - Flora Tassone) – *Panel: Elizabeth Berry-Kravis, Randi Hagerman* – Targeted Treatments in Other Neurodevelopmental Disorders	*Zoom*
21:00 onwards		**Post-session Social event** – Virtual Coffee / Bar	*Gather*

Abstracts for Research Symposium 9th – 10th September *(in order of presentation)*

1. KEYNOTE: Reimagining Autistic Education: Lessons Learnt From Remote Learning During Lockdown

Liz Pellicano
Macquarie University

During the early stages of the COVID-19 pandemic, more than a billion students around the world were taken out of schools during associated lockdown restrictions and thrust into learning-from-home contexts. Many students faced intense educational challenges during this time, when schools and teachers rapidly sought to move curricula online. The disruption, however, is likely to have had a disproportionate impact on those who might already be vulnerable in some way – including autistic children and young people. In this talk, we draw on data from a large-scale qualitative and participatory study with Australian young autistic people and families to understand how the experience impacted upon them, and how the findings might inform the ways in which autistic children might flourish at school in more 'normal' times.

2: Wearable Digital Gait-Based Outcome Measures for Children With Fragile X, Prader-Willi and Angelman Syndromes

***Kraan C.M.*[1,2], *Date P.*[1], *Baker E.K.*[1,2], *Rattray A.*[1], *Sangeux M.*[3], *Amor D.J.*[1,2,4], *Godler D.E.*[1,2]**

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Background: Fragile X syndrome (FXS), Prader-Willi syndrome (PWS) and Angelman syndrome (AS) are neurogenic disorders in need of new innovative solutions for treatment evaluation and monitoring. Quantitative gait analysis offers a potentially useful approach to measure neurological and motor dysfunction in these groups. However, because traditional approaches such as electronic walkways and motion capture setups require adherence to instructions, which can be problematic for these groups, different non-traditional gait analysis paradigms require exploration. This study examines feasibility and construct validity of targeting steady-state gait patterns in "real-world" non-laboratory wearables gait data collected from brief two-minute assessments in children who have FXS, PWS, AS and controls of a similar age and sex.

Methods: In this study, children diagnosed with FXS (n=11), PWS (n=7) and AS (n=5), (~48% female; 6-16 years) and 22 neurotypical controls of the same age range/sex-ratio completed non-laboratory walking assessments with shoe-attached Gait Up wearable sensors. Spatiotemporal data were extracted using a novel gait segmentation algorithm that targeted steady-state gait. Extracted data were the mean (leg-length corrected) and variability results for stride time, cadence, stance time, stride length and heel strike angle.

Results: The sensors were well tolerated, and the longer walk allowed patients time to be comfortable during the assessment. Each group diverged from controls on all measures of stride variability (all $p < 0.05$). There were also syndrome-specific profiles in mean gait results indicating different compensation strategies.

Conclusions: Gait analysis measured outside the laboratory was feasible and straightforward for each studied disorder and the targeted steady-state data demonstrated construct validity. Findings warrant further investigation of wearable digital gait-based outcome measures in children with FXS, PWS and AS and potentially other disorders characterised by neurological and/or motor dysfunction.

Keywords: Fragile X syndrome, Prader-Willi syndrome, Angelman syndrome, wearable technology, gait analysis, outcome measures

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3: Sleep and Behaviour in Children With Tuberous Sclerosis Complex: A Remote Study Using Actigraphy and Mobile App Technology

Bissell S.L.[1]*, Williams C.*[2]*, Oliver C.*[1]*, Bagshaw A.P.*[1]*, Wilde L.V.*[3]*, de Vries P.J.*[4]*, Hill C.*[5]*, Richards C.R.*[1]

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Background: Tuberous sclerosis complex (TSC) is a multisystem neurodevelopmental disorder characterised by benign tumour growth, epilepsy, autism and painful physical health conditions. Based on informant-report questionnaires, children with TSC evidence significant settling problems, night-waking and elevated daytime sleepiness compared to typically developing (TD) children. To date, only one small-scale direct single night study has been conducted to explore the profile of sleep in children with TSC. The present study aimed to advance previous research by utilising both questionnaire and direct measures of sleep across multiple nights, and exploring potential associations between poor sleep and daytime behaviours.

Methods: Caregivers of 20 children aged 4-15 years with TSC completed informant-report measures of sleep and behaviour. Actigraphy was employed as a direct measure of sleep for a minimum of seven nights. Informant-report information and actigraphy data from an age and sex-matched TD group were utilised to compare sleep profiles between children with TSC and TD children. Caregivers of children with TSC also completed mobile app sleep, pain, seizure and behaviour diaries across consecutive mornings and evenings.

Results: Children with TSC obtained higher informant-report daytime sleepiness scores compared to TD children ($p < .01$), but did not evidence significant differences on objective sleep parameters measured using actigraphy (e.g. sleep efficiency, wake after sleep onset). Objective sleep parameters also did not differ between nights of highest and lowest seizure activity in the TSC group. However, actograms of several children with TSC indicated a fragmented morning sleep pattern of early waking and late morning napping.

Conclusions: Although few overall TSC-TD group differences were observed, this study highlights the importance of adopting a multifaceted and individualised approach to sleep research in TSC. Late morning napping and daytime sleepiness may be associated with seizure activity in TSC, and therefore the adverse effects of antiepileptic medications warrants further investigation.

Keywords: Tuberous sclerosis complex, TAND, sleep, behaviour, actigraphy, epilepsy

4: The Research Landscape of Tuberous Sclerosis Complex-Associated Neuropsychiatric Disorders (TAND) – A Comprehensive Scoping Review

Vanclooster S.[1], Bissell S.[2], Heunis T.[1], Jansen A.[1,3], de Vries P.J.[4], the TAND Consortium

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Background: Tuberous Sclerosis Complex Associated Neuropsychiatric Disorders (TAND) is an umbrella term for behavioural, psychiatric, intellectual, scholastic, neuropsychological and psychosocial manifestations in TSC. Although TAND affects 90% of individuals with TSC during their lifetime, these manifestations are relatively under-identified, under-treated and under-researched. This comprehensive scoping review describes the existing TAND research landscape to identify knowledge gaps that could guide recommendations for future TAND research.
Methods: The Arksey & O'Malley (2005) scoping review methodology was used to answer eleven research questions related to publication year, study location, participant age, study quality, TAND manifestation focus and study design.
Results: Of 2,841 returned searches, 230 articles were included (30 animal studies, 47 case studies, 153 cohort studies). Studies were published between 1987 and 2020 with 52% published since 2013. Research sites included 45 countries, predominantly high-income countries such as the USA (26%) and UK (15%), with only 14% from low/middle-income countries (LMICs). Studies predominantly involved children (n = 97) and adolescents (n = 96) as opposed to older adults (n = 24). Of the 153 cohort studies, only 16 were interventional (10%), 13 of which were pharmacological or mTOR inhibitor clinical trials. Few cohort studies used remote technologies (n = 13). Animal and case studies were of relatively high quality, while cohort studies showed considerable variability in quality. Across human studies, the intellectual level had most research (n = 126; 72%) and the academic level least (n = 57; 25%).
Conclusions: Despite the increase in TAND research, various knowledge gaps were identified. Areas for future research include older adulthood, the full range of TAND manifestations, LMICs, and non-pharmacological intervention studies. The quality of cohort studies requires improvement to which the use of standardised measurements including direct behavioural assessments may contribute. Utilisation of remote technologies could address many of the TAND knowledge gaps.

Keywords: Tuberous Sclerosis Complex, neuropsychiatric disorders, scoping review, knowledge gaps, priority-setting and recommendations

5. KEYNOTE: Developmental Science and Treatment Innovation

Jonathan Green
University of Manchester

In this lecture I will take a transactional approach to neurodiversity, with autism as a particular example, and suggest how this is a gateway into intervention models. I suggest the more that we understand about the impact of neuro diverse development on transactional processes (with others and with the environment) the more we will be able to model specific and effective intervention paradigms at different ages. Experimental mechanistic tests of such interventions can in turn feedback in a crucial way to help us understand development more clearly.

In the specific example of infants at risk of later autism, observational research suggests indeed a general perturbation of normally constrained dyadic interaction processes, which seem cascading and by 14 months predict later autism development. This thinking forms the basis of the pre-emptive intervention strategies that we developed in infancy (iBASIS), and a post-diagnostic strategy for diagnosed children in the pre-school and early school years (PACT); both of which have shown sustained developmental effects to improve autism symptom functioning. In mechanistic study, both studies show a two-stage cascade of effect; firstly, into changes in the early dyadic environment of the child, and secondly the child's generalisation of such dyadic experience into altered social functioning in other contexts. I will discuss what tells us about the mechanisms at work in each of these stages, and whether adjunctive approaches might amplify such effects. Work in ADHD is here an interesting comparator.

Finally, I will locate such intervention strategies in terms of autistic experience in the wider world. Autism intervention has been criticised by some advocates as an attack on autistic identity, but these transactional approaches seem generally to be experienced as respectful of autistic difference. Similar models of environmental adaptation map onto wider issues of disability rights.

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6: Atypical Visual Attention Predicts Emerging Autistic Traits in Infants With Tuberous Sclerosis Complex

***Tye C.*[1,2], *Runicles A.K.*[1], *Mason L.*[3], *Charman T.*[2], *Johnson M.H.*[4], *Jones E.J.H.*[3], *Bolton P.F.*[1]**

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Background: Up to 60% of individuals with tuberous sclerosis complex (TSC) meet diagnostic criteria for autism spectrum disorder (ASD). The majority of studies examining correlates of ASD in TSC have been conducted after a diagnosis of ASD has been established. Altered visual attention predicts ASD diagnosis in infants who have an elevated familial likelihood for ASD. This study aimed to: (1) characterise developmental trajectories of visual attention, and (2) identify visual attention predictors of emerging ASD traits, in infants with TSC.
Methods: The Early Development in Tuberous Sclerosis (EDiTS) Study is a prospective longitudinal study of infants with TSC (total n=32) and typically developing infants (TD; total n=34). Infants are seen at home up to 7 times between 3 and 24 months, and are administered a battery of eye-tracking tasks using portable technology. We measured efficiency of attention disengagement from a central visual stimulus to a peripheral target in a gap-overlap task. At 18 and 24 months, parents completed the Quantitative Checklist for Autism in Toddlers.
Results: Linear mixed models revealed a main effect of group on attention disengagement ($p=.005$). Post-hoc tests revealed infants with TSC showed longer disengagement times at 10 and 14 months only ($p<.05$). A significant group x time interaction indicated slower and delayed increases in the speed of disengagement over development in TSC ($p=.002$). Longer disengagement times at 10 months old were associated with emerging ASD traits at 18-24 months in both the TD ($rho=.58$, $p=.03$) and TSC groups ($rho=.50$, $p<.05$).
Conclusion: Infants with TSC take longer to disengage their attention and show an atypical developmental trajectory of attention disengagement. Slower disengagement in infancy is associated with ASD traits in early toddlerhood. Identifying objective infant markers of ASD in TSC will aid in targeting early intervention and providing a read-out of intervention efficacy.

Keywords: Autism spectrum disorder, eye-tracking, infants, longitudinal, tuberous sclerosis complex, visual attention

7: Longer Term Tolerability and Efficacy of ZYN002 Cannabidiol Transdermal Gel in Children and Adolescents with Autism Spectrum Disorder (ASD): An Open-Label Phase 2 Study (BRIGHT [ZYN2-CL-030])

***Heussler H.*[1,2], *Duhig M.*[1,2], *Hurst T.*[3], *O'Neill C.*[4], *Gutterman D.*[4], *Palumbo J.M.*[4]**

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Background: ZYN002 is a pharmaceutically manufactured transdermal cannabidiol gel. BRIGHT is a single-center, open-label phase 2 study evaluating the tolerability and efficacy of ZYN002 in children/adolescents aged 3-17 years with ASD.

Methods: Patients with Clinical Global Impression (CGI)–Severity scores ≥4 (moderate or greater) and Aberrant Behavior Checklist-Community (ABC-C) Irritability scores ≥18 were enrolled. Patients received ZYN002 250 or 500 mg/day on top of stable standard of care. Patients demonstrating ≥35% improvement in Irritability at week 14 were allowed to continue treatment. Safety assessments included adverse events (AEs), laboratory tests, and electrocardiograms (ECGs).

Results: 37 patients (mean age: 9.2 years) enrolled; 94% had moderate-to-severe symptoms; the mean baseline ABC-C Irritability score was 30.3. At week 14, significant improvements (P ≤0.0053) were observed for each ABC-C subscale, the Parent-Rated Anxiety Scale-ASD (PRAS-ASD) score, the Autism Parenting Stress Index (APSI) score and each Autism Impact Measure (AIM) domain in 28 who completed week 14. 57% of patients were improved ("much/very much improved") based on CGI-Improvement (CGI-I). Eighteen patients demonstrated ≥ 35% improvement in Irritability and elected to continue. At week 38, improvements in the ABC-C subscale scores (50% to 61% across domains; P<0.0001), the PRAS-ASD (42%; P<0.0001), APSI (40%; P<0.0001) and the AIM (19% to 36% across domains; P≤0.0008) were maintained. 77% were improved on the CGI-I. 54% of patients reported AEs. AEs were mild (80%) or moderate (20%). Treatment-related AEs were reported in 19% of patients; most were mild and transient. One patient discontinued due to application site reaction. No serious or severe AEs or clinically significant changes in laboratory tests or ECGs were reported.

Conclusion: BRIGHT provides initial evidence suggesting a positive risk–benefit profile for ZYN002 when added on top of stable standard of care in children/adolescents with ASD which was maintained over 38 weeks. Further studies are warranted.

Keywords: Autism, cannabidiol, irritability, core-symptoms, safety, efficacy

8: Autism-Related Phenotypes in Genetic Syndromes

Bozhilova N.[1,2]*, Welham A.*[3]*, Adams D.* [4]*, Bissell S.*[2]*, Bruining H.*[5]*, Crawford H.*[6,2]*,Eden K.*[2]*, Nelson L.*[2]*, Oliver C.* [2] *, Powis L.*[2]*, Richards C.*[2]*, Waite J.* [7,2]*, Wilde L.*[8]*, Woodcock K.*[2]*, Moss J.*[1,2]

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Background: Early phenotypic studies have identified that genetic syndromes give rise to distinct patterns of autistic characteristics, leading to diagnostic uncertainty and limited access to autism-related support. However, these early studies have tended to include relatively small sample sizes and to position a single syndrome group of focus in contrast with a small number of comparison populations.

Methods: Autism-related profiles (based on Social Communication Questionnaire (SCQ) scores) were evaluated across thirteen genetic syndrome groups (Angelman n=154, Cri du Chat n=75, Cornelia de Lange n=199, Fragile X n =297, Prader-Willi n=278, Lowe n=89, Smith-Magenis n=54, Down n=135, Sotos n=40, Rubinstein-Taybi n=102, 1p36 n=41, Tuberous Sclerosis Complex n=83 and Phelan-McDermid n= 35syndromes). It was hypothesised that each syndrome group would evidence a distinct autism profile. To test this hypothesis, a classification algorithm via support vector machine (SVM) learning was applied to over 1500 individuals diagnosed with one of the thirteen genetic syndromes (Mean age: 16 years; Total Self-help score: 6.53). The SVM algorithm was also applied to a sample of autistic individuals who did not have a known genetic syndrome (ASD-NS; n=254). Self-help skills and age were included as additional predictors.

Results: Overall, the genetic syndromes were associated with specific SCQ/autism profiles, indicated by the substantial accuracy of the entire SVM model (55%). Nevertheless, certain syndrome groups (i.e., Angelman, Fragile X, Prader-Willi, Rubinstein-Taybi and Cornelia de Lange) showed greater behavioural specificity than others (i.e., Cri du Chat, Lowe, Smith-Magenis, Tuberous Sclerosis Complex, Sotos, Phelan-McDermid). The inclusion of the ASD-NS reference group, self-help skills and age did not change the model accuracy.

Conclusions: Findings extend previous work, demonstrating syndrome specific and atypical SCQ/autism profiles in genetic syndromes. SVM algorithms can also be used to determine the specificity of autism-related profiles in individuals with genetic syndromes.

Keywords: Autism, Genetic Syndromes, Machine Learning, Phenotypes

9. KEYNOTE: From Impossible to Possible: A Personal Journey From Diagnosis Through Drug Development for Angelman Syndrome.

Allyson Berent
Foundation for Angelman Syndrome Therapeutics (FAST)
The Animal Medical Center, New York City

In 2014 everything changed. The life of a successful veterinary specialist designing medical devices and enthralled in clinical research for animals came to a screeching halt. My little girl Quincy, 5.5 months old, was diagnosed with a random, rare, neurogenetic disorder called Angelman syndrome (AS). Through pure passion, scientific understanding, and medical education, I knew a treatment for this disorder was possible, with the understanding there was absolutely no approved therapeutics. After countless conference calls, scientific stalking, and a dream, I started my journey from becoming a fierce advocate, the Chief Science Officer of the largest non-governmental research funding foundation in AS in the world (FAST), to the co-founder and Chief Operating Officer of GeneTx Biotherapeutics, focused on developing an antisense oligonucleotide for the treatment of Angelman syndrome. The foundation funded an academic lab to develop this ASO and deeply understand the unique phenomenon associated with AS (imprinting). This funding resulted in the discovery of a unique genetic region that could be exploited, essentially turning on the gene missing in neurons of those with AS. It was at that time that the foundation decided to advance the development of this potential disease modifying therapeutic, recruit some of the most experienced experts in ASO drug development in the world, and drive the program for a first in human clinical trial. Through determination, supportive expertise, and amazing consultants, GeneTx completed IND enabling studies and launched a clinical trial for FIH in 2020. The vision and dedication of parents and loved ones drove this program, allowing the team to remain singularly focused on a population approximating 1:15,000.

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10: Genes to Mental Health Network Report: Stakeholders Perspectives on Research Participation

T. Blaine Crowley [1], Lauren White [1], Brenda Finucane [2], Sixto Garcia-Minaur [3], Gabriela Repetto[4], Matthias Fischer [5], Sebastien Jacquemont [6], Raquel Gur [1], Anne Maillard [7], Kirsty Donald [8], Anne Bassett [9], Ann Swillen [10], and ***Donna M. McDonald-McGinn*** *[1]*

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[8] *Red Cross War Memorial Children's Hospital, Cape Town, South Africa*

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[10] *KU Leuven, Leuven, Belgium*

Background: Research participant feedback is rarely collected; thus, investigators have limited understanding regarding motivation to participate. The G2MH Network surveyed eligible stakeholders affected by copy number variations (CNVs), including 22q11.2, regarding incentive for study involvement and opinions concerning research priorities.

Methods: A REDCap survey was built in English on instruments from Vanderbilt and EURORDIS, translated into 11 languages using DeepL software/native speakers, and distributed by 22 advocacy groups including 22q11.2 organizations.

Results: 1,035 people responded from 29 countries. 704 completed the entire survey. 44% previously participated in research. Most respondents were mothers of children with 22q11.2 CNVs. Top reasons for initial participation included compensation, provider encouragement, free healthcare, and positive previous experiences. Motives for leaving included treatment risks and result non-disclosure. Main motivations to remain in research studies were access to care/information, helping others, and improving quality of life. Importantly, participants wanted summaries of results/labs and flexible schedules.

Conclusions: This study provides invaluable insights for planning research studies in partnership with stakeholders. Payment was an initial motivator for joining, as was encouragement from a clinician or caregiver, but participants ranked non-monetary benefits as reasons to remain engaged in research. Notably, satisfaction was high overall for those previously participating in studies. Stakeholders identified lack of public funding for rare disease research, lack of public awareness, difficulty in generating interest in participation, and a paucity of study subjects due to disease rarity as obstacles to supporting such investigations. G2MH hopes to address these issues by analysing data across rare CNVs including 22q11.2.

11: Parental Perception of Emotional/Behavioural Problems in Brazilian Children and Adolescents With Williams Syndrome

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Background: Williams Syndrome (WS) is a rare multisystemic genetic disorder caused by a hemizygous deletion of approximately 1.6 megabases (Mb) on chromosome 7q11.23 and a prevalence of 1:7500 births. Individuals with WS are likely to present developmental delays and emotional and behavioural problems (EBP). The aim of this study was to assess EBP among children and adolescents with WS in a Brazilian sample.

Methods: The sample comprised of 56 children and adolescents (33 boys) aged 8.09 – 17.91 (mean 13.87 years, median: 14.12, SD: 2.64). The rating scale used to assess EBP was the Child Behavior Checklist (CBCL/6-18), while cognitive functioning was assessed by administering one of the following: Wechsler Intelligence Scales for Children/versions III and IV (WISC-III and WISC-IV) in the short forms, and the Wechsler Abbreviated Scales of Intelligence (WASI).

Results: The mean Wechsler IQ was 52.91 (median: 50.00, SD: 11.08, range: 40–89). Older age was significantly associated with higher T-Scores in the Internalizing Problems scale ($r_s = .35$, $p = .009$). No gender differences were found for any of the CBCL Empirically Based Scales, Higher-Order Factors or DSM-Oriented Scales, except for the Anxiety Problems scale in which boys scoring significantly higher than girls ($Z = -2.85$, $r = .38$, $p = .004$). Between 20% and 55% of the individuals had T-Scores in the borderline or clinical range on the empirically based scales of Thought Problems (55.1%), Attention Problems (32.1%), and Social problems (21.4%). No correlations were found between CBCL T-scores and IQ.

Conclusion: The CBCL reflected parental interpretations of EBP. For this sample, the older children showed the higher Internalizing T-Scores. The data suggested that boys would have higher indicators of emotional characteristics compatible with several psychopathologies. These findings reinforce the necessity of additional studies in WS to better organize and conduct psychological and behavioural interventions programs.

Keywords: Williams Syndrome, emotional behavioural problems, CBCL, neuropsychological testing.

12: Williams Syndrome: On the Role of Intellectual Abilities in Anxiety

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Background: The William syndrome (WS) phenotype is associated with high levels of anxiety, and a unique behavioural profile, with strengths in verbal and social domains, combined with significant executive difficulties. Most previous studies on anxiety in WS are based on questionnaire data. The aim of this study was to use direct measures to investigate the effects of general intelligence, executive functions, and attentional abilities on anxiety in WS, considering age effects.

Method: The study participants were 24 individuals with WS (mean age: 29 years, range: 9-53 years), and their parents. The MINI international neuropsychiatric interview for DSM-5 was completed to establish clinical diagnoses of anxiety, and the Clinical Global Impression Scale – Severity was used for rating of symptom severity. Intellectual abilities were measured using the Wechsler scales, and attention and inhibition using the Conner's Continuous Performance Test. In addition, the parent reported Five-to-Fifteen questionnaire was collected for scores on executive functions, learning and memory.

Results: In contrast to our hypothesis, we found no association between anxiety and core elements of executive functions, such as working memory, sustained attention, and inhibition. Using ordinal logistic regression analyses, we showed that decreasing IQ and age combined, are associated with elevated anxiety. We confirmed these results in between-groups analyses (anxiety disorder vs no anxiety disorder), and that low IQ was associated with higher risk of having an anxiety diagnosis. To further corroborate the associations, we used Bayesian statistics and found substantial evidence for the null hypothesis for the associations between anxiety and learning difficulties, as well as anxiety and inhibition.

Conclusion: Based on direct measures (i.e. clinical assessments and psychological testing), our results provide a deeper characterisation of the WS phenotype, and insights to the mechanisms underpinning anxiety in WS.

Keywords: Williams syndrome, IQ, intellectual abilities, executive functions, anxiety, behavioural phenotype

13: Child Characteristics Associated With Parental Stress and Child/Parental Quality of Life in Angelman Syndrome

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Background: Angelman syndrome (AS) family studies report increased parental stress and lowered child- and parental Quality of Life (QoL). Child characteristics may be key in the level of parental stress and child/parental QoL, however there is a lack of data relating the two. The current study investigates whether and how sleep problems, developmental level, or autistic features of children with AS are associated with parental stress and child/parental QoL outcomes.

Methods: We retrospectively collected data from clinical assessments of paediatric AS patients (n=73, mean age=9.2 years) at the ENCORE Angelman expertise centre (Erasmus MC Sophia, Rotterdam, the Netherlands). A linear regression analysis was conducted for the following dependent variables: parental stress (short Dutch version of the parental stress index–NOSI-K) and child/parental QoL (all subscales of the short Infant Toddler Quality of Life questionnaire–ITQOL-SF47). Independent variables were sleep problems (Sleep Disturbance Scale for Children–SDSC), level of cognitive development (Bayley-III-NL cognition scale), and autistic features (Autism Diagnostic Observation Schedule–ADOS Calibrated Severity Score). Gender, age, genotype and epilepsy were included as child covariates.

Results: Preliminary results show that a higher SDSC total score was significantly associated with a lower score on the ITQOL subscales 'Physical Abilities', 'Bodily Pain' and 'Parental Impact – Time'. Effect sizes were medium to large. The ADOS and Bayley-III-NL scores were not related to NOSI-K or ITQOL scores. The SDSC score was not related to the NOSI-K score.

Conclusion: We found child sleep disturbances to be associated with lower child QoL. In addition, child sleep disturbances are related to parents experiencing more limitations in the time to attend their own personal needs (due to the impact of the child's syndrome). These results suggest that more focus on improving child sleep disturbances is needed in order to improve child- and parental QoL in AS.

Keywords: Angelman syndrome, Quality of Life, parental stress, sleep problems, developmental level, autistic features

14. KEYNOTE: Intellectual Ability Based Phenotypes in Autism Spectrum Disorders From Early Childhood to Preadolescence.

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Previously, our laboratory has examined the longitudinal development of intellectual ability level (IQ). We have been motivated to investigate IQ given that it is the strongest predictor of outcomes in individuals with autism spectrum disorder (ASD) and typical development, and that it constitutes the most significant source of heterogeneity within the ASD phenotype. We analysed data from the longitudinal Autism Phenome Project (APP) cohort, and identified four distinct IQ trajectories in a sample of ASD youth from early (ages 2-3.5 years) to middle (ages 5-8) childhood (*What Will My Child's Future Hold? Phenotypes of Intellectual Development in 2–8-Year-Olds with Autism Spectrum Disorder*; Solomon et al., 2018). Baseline and developmental course differences among groups of participants with autism were assessed using univariate techniques and repeated measures regression models. A four-class model best represented the data, with participants assigned to High Challenges (25%), Stable Low (18%), Changers (35%), and Lesser Challenges (22%) groups. The Changers group demonstrated the most significant IQ change (>2 SDs) that was accompanied by adaptive communication improvement and declining externalizing symptoms. Only the Lesser Challenges group showed a significant reduction in ASD symptom severity. My address at SSBP will report the results of our recent attempts to extend this analysis to preadolescence/early adolescence (ages 9-13) to see if the same subgroups persist and if they are significant predictors of more distal outcomes. This talk reports these results. Latent class growth analysis are used in both autism and non-autism groups. Linear and quadratic age-based models are be tested. We largely replicate our original study and show there are three distinct IQ trajectories in the current sample's ASD group which extended into preadolescence. Results pertaining to whether membership in these adolescent subgroups predicts adaptive communication and internalizing and externalizing behaviour also will be presented.

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15: The Effect of Early Hormonal Treatment (EHT) on Neuromotor Capabilities in Infants and Toddlers with 47,XXY

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Background: 47,XXY is characterized by reduced androgen levels, language-based learning difficulties, developmental dyspraxia, and neuromotor dysfunction. In recent studies, early hormonal treatment (EHT) has been shown to potentially mitigate some of these deficiencies. In this study, we investigated the role of EHT on neuromotor skills in a large cohort of infants and toddlers with 47,XXY.

Methods: Two-hundred and twenty-nine boys diagnosed prenatally with 47,XXY between the ages of birth and 2 years, 11 months were administered the fine motor, gross motor, and psychomotor developmental index (PDI) subtests of the Bayley Scales of Infant Development (BSID). For statistical analysis, the cohort was segregated by age: birth to 11 months, 12 to 23 months, and 24 to 35 months. Within each age group, subjects were further bifurcated into two treatment groups: No-T (N= 140) and EHT (N= 89). Two-tailed t-tests were performed to analyse statistically significant differences between treatment groups.

Results: In all three age groups, the EHT infants and toddlers performed significantly better on the PDI scale than the No-T boys (birth to 11 months, p=0.0001; 12-23 months, p=0.0525; and 24-35 months, p=0.0024). >From birth to 11 months, the EHT group had a mean of 102.46 while the No-T group had a mean of 98.07. Additionally, the EHT group scored significantly better on the fine motor subtest of the BSID than the No-T group for birth to 11 months (p=0.0235).

Conclusion: Consistent with the literature, untreated 47,XXY boys showed reduced fine motor scores. Our findings of significantly better performances on the BSID-PDI among treated boys in every age group suggest EHT may be essential in optimizing the outcome for neuromotor development in 47,XXY boys during infancy and early childhood years. This may be critical for mitigating the often associated and pervasive developmental dyspraxia and dysgraphia in older 47,XXY boys.

Keywords: 47,XXY, Klinefelter syndrome, early hormonal treatment (EHT), neuromotor, sex chromosome aneuploidy

16: Incidence of Mental Health Disorders and Behavioural Complications in a Large Cohort of Teenagers with 47,XXY (Klinefelter Syndrome)

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Background: 47,XXY occurs in approximately 1:600 live male births and is believed to have an increased incidence of ADHD and anxiety disorders. This study reports on a large cohort of males with 47,XXY between 12 and 18 years and occurrence of diagnosed psychological disorders, psychiatric hospitalizations, and legal/school difficulties. This study analyses the potential impact of timing of diagnosis and status of testosterone treatment.
Methods: Detailed, 3-generation pedigree family histories were collected for 122 teenagers with 47,XXY between 12 and 18 years. Psychiatric diagnoses were made by outside licensed professionals. The cohort was separated into four groups depending on timing of diagnosis and testosterone treatment (Group A (n = 55): prenatally diagnosed and untreated; Group B (n = 42): prenatally diagnosed and treated; Group C (n = 14): postnatally diagnosed and untreated; Group D (n = 11): postnatally diagnosed and treated). One-way ANOVA and post-hoc analyses using the Bonferroni procedure were used.
Results: Of 122 teenagers, 43.44% had no psychiatric history. 23.46% were diagnosed with ADHD, 31.97% with anxiety disorder, 7% with depression, and 1.64% with Autism Spectrum or Bipolar Disorder. Four boys (3.28%) had history of psychiatric admissions. Two boys (1.64%) experienced legal trouble. In addition, three boys (2.46%) had a school suspension/expulsion. There was no difference between the four groups for occurrence of familial psychiatric history.
One-way ANOVA identified differences within the incidence of any psychiatric disorder (p=0.007). Post-hoc analysis revealed a significant difference between Groups B and D, with Group B having less psychiatric diagnoses (p=0.012).
Conclusion: This study identified an increased incidence of psychiatric disorders in postnatally diagnosed males with 47,XXY. This finding outlines the positive effect of early detection and intervention on mental health and behaviour in these males. Supplemental research is needed to investigate the risk of emergence of psychiatric disorders in this population.

Keywords: Klinefelter Syndrome, Mental Health, Sex Chromosome Aneuploidies, 47,XXY, ADHD

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17: The eXtraordinarY Babies Study: Early Developmental and Adaptive Functioning Profiles of Infants and Toddlers with Prenatally Identified Sex Chromosome Trisomies

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Background: The eXtraordinarY Babies Study is a prospective study of infants diagnosed prenatally with sex chromosome trisomy (XXY, XYY, Trisomy X) designed to identify predictors of the variable neurodevelopmental and health outcomes in these conditions. Developmental profiles are characterized utilizing a combination of direct developmental assessments and parent report of skills in their naturalistic environment. Here we present early developmental data from the first cohort of participants.

Methods: Infants with XXY, XYY, or XXX (n=130) were assessed using a battery that included the Bayley Scales of Infant Development–3 and Vineland-3 at 6, 12, and 24 months of age. One sample t-tests compared sub-domain scores to population means, and paired sample t-tests compared sub-domain composites at each timepoint (expressive vs. receptive language and fine vs. gross motor). Repeated measures ANOVAs explored scores across timepoints.

Results: Bayley-3 results showed no differences in cognitive skills compared to population mean at all timepoints (cognitive scaled score mean(SD): 6m=9.8(2.7); 12m= 10.6(2.1); 24m=10.6(2.5)). Expressive and receptive language were lower than population mean ($p \leq .001$) at 6 and 12 months (however still within the typical range), with improvement for receptive language by 24 months of age but persistently lower expressive language ($p < 0.01$). Motor profiles showed typical fine motor skills across timepoints, with gross motor lower than population means and fine motor at all timepoints ($p \leq .01$). Parent report from the Vineland-3 showed the same pattern of scores, however with improved gross motor scores at 24 months.

Conclusion: Results identify domains of expressive language and gross motor as the most consistently impacted through 2 years of age, suggesting these domains as targets of monitoring and intervention in the first years of life. Next steps include analysis of the role of early interventions, medical history, and other factors such as early hormone levels in developmental trajectories and outcomes.

Keywords: Sex chromosome disorder, xxy, xyy, trisomy X

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18: An Intervention to Support Families Affected by Fetal Alcohol Spectrum Disorder (FASD) in a Remote Australian Indigenous Community

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Background: The West Kimberley region of Australia was previously identified as having a high prevalence of FASD. Families reported the major behaviour problems recognised as typical of FASD. Indigenous Triple P has been shown to be effective in other remote communities in Australia.
Methods: We partnered with local indigenous organisations to deliver a locally modified version of the indigenous Triple P program. The program was delivered to the whole community by trained local community members.
Results: The program resulted in improvements in children's behaviour, and parental confidence and parenting style. The success of the program resulted from a number of specific factors which give good guidance for public health interventions in indigenous communities coping with historical trauma.
Conclusions: Indigenous Triple P should be made available more widely, as long as implementation is locally led and supported by other health and social programs.

Keywords: Fetal Alcohol Spectrum Disorder, indigenous communities, parent training.

19: The Relationship Between Sensory Sensitivity and Maladaptive Behaviours in Children with Cornelia de Lange Syndrome

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Background: Cornelia de Lange Syndrome (CdLS) is a rare genetic disorder caused by malformation of cohesin-related genes. These mutations produce multisystem developmental anomalies and abnormal sensory processing. In addition, individuals with CdLS display maladaptive behaviours such as repetitive and self-injurious tendencies. Individuals with autism spectrum disorder, for which CdLS is a model disorder, have phenotypic sensory processing deficits. We examine the relationship between sensory processing and maladaptive behaviours in a cohort of children with CdLS to delineate the use of sensory domains in phenotyping CdLS.
Methods: Children with CdLS were administered the Dunn Sensory Profile to assess sensory hyper- and hyposensitivity responses to stimuli. Dunn subscales are comprised by tactile, auditory, visual, vestibular, multisensory and oral scores. The Aberrant Behaviour Checklist Community version (ABC-C) assessed behavioural dysregulation across domains including irritability (mood dysregulation, aggression), lethargy (depression, decreased socialization), hyperactivity, stereotypies (repetitive behaviours, rigidity) and speech abnormalities. CdLS diagnoses were ascertained clinically by a geneticist.
Results: 41 children with CdLS, ages 10.8 ± 3.8 yrs and 44% were male, comprised the sample. Stereotypies is significantly correlated with vestibular (p= 0.044), tactile (p=0.039), and multisensory (p=0.001) domains. Lethargy is significantly correlated with tactile (p=0.009) and multisensory (p=0.001) domains. Irritability is associated with tactile (p = 0.012) and multisensory (p = 0.010) domains. Hyperactivity is associated with auditory (p = 0.007), tactile (p = 0.001) and multisensory (p = 0.007) domains. ABC total score was significantly associated with tactile (p = 0.001), auditory (p = 0.022) and multisensory domains (p = 0.001).
Conclusion: The behavioural phenotype of CdLS should include a characterization of sensory processing in relation to behavioural domains, with tactile and multisensory domains being most salient in relation to lethargy, hyperactivity and irritability. Pathways that interrelate these sensory and behavioural domains remain an area of active research in CdLS and autism.

Keywords: Cornelia de Lange syndrome, sensory processing, maladaptive behaviours, tactile sensitivity

20: The Behavioural Profile of Children With Sex Chromosome Trisomy: Neurocognitive Underpinnings of Behavioural Outcomes

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Background: Individuals with sex chromosome trisomy (SCT) have an elevated risk for neurobehavioral problems. However, not much is known about neurobehavioral outcomes in very young children. As neurobehavioral problems may arise as a consequence of different information processing deficits, it is important to not only focus on neurobehavioral outcomes in young children, but also on neurocognitive functions as possible underlying mechanisms in explaining these outcomes. The neurocognitive function of interest in this presentation is language, including structural language and use of language in a social setting (i.e., pragmatic language).

Methods: The TRIXY early childhood study is a longitudinal study, based at Leiden University the Netherlands in collaboration with the eXtraordinarY Kids Clinic in Denver Colorado. Children aged 1-7 years were included (NSCT = 103, NControl = 102). Social-emotional functioning, behavioural outcomes and various language abilities were assessed.

Results: (Preliminary) results demonstrate that (1) Behavioural problems, including social-emotional problems, affective problems, pervasive developmental problems can occur in children as young as 1-3 years old (2) Social-emotional problems may require special attention as these problems seem most prominent, showing increased risk across the 1-5-year age range, regardless of timing of diagnosis, and across all three SCT karyotypes (3) Language difficulties can be present in very young children with SCT, on various domains, including receptive and expressive semantic skills and pragmatic abilities and (4) Language outcomes, in particular the social use of language, are predictive for later behavioural problems, most prominently for pervasive developmental problems, social-emotional problems, and attention-deficit problems.

Conclusion: This study demonstrates the importance of early screening in routine clinical care for children with SCT and illustrates the importance of monitoring not only structural language development, but more global communication development as well as these neurocognitive functions could serve as markers to identify children at-risk for aberrant development.

Keywords: Sex Chromosome Trisomy, Behavioural Problems, Structural Language, Pragmatic Language, Early Childhood

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21: Neurodevelopmental and Psychiatric Disorders in Females With Turner Syndrome: A Population-Based Study

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Background: Turner syndrome is the result of a missing X chromosome, partially or completely, in phenotypic girls. This can cause an array of medical and developmental difficulties. The intelligence quotient has previously been described as uneven but considered within normal range. Although a social, intellectual and psychiatric profile is described in females with Turner syndrome, it is unclear to what extent they meet the clinical criteria for neurodevelopmental or psychiatric diagnoses. The aim of this study was to examine the prevalence of neurodevelopmental and psychiatric disorders in females with Turner syndrome.

Methods: A retrospective case-control study was performed with a total of 1392 females with Turner syndrome identified through the Swedish National Patient Register and compared with 1:100 age- and sex matched controls from the general population. The association between Turner syndrome and diagnoses of neurodevelopmental and/ or psychiatric disorders were calculated using conditional logistic regression and is presented as estimated risk (Odds ratio, OR, 95% Confidence interval, CI) in females with Turner syndrome compared with matched controls.

Results: Females with Turner syndrome had higher risk of any neurodevelopmental or psychiatric disorder (OR 1.37, 95% CI 1.20-1.57), an eightfold (OR 8.59, 95% CI6.58-11.20) increased risk of intellectual disability and a fourfold (OR 4.26, 95% CI 2.94-6.18) increased risk of autism spectrum disorder compared with the controls. In addition, females with Turner syndrome had an increased risk of a diagnosis of psychotic disorders (OR 1.98, 95% CI 1.36-2.88), eating disorders (OR 2.03, 95% CI 1.42-2.91) and behavioural disorders (OR 2.01, 95% CI 1.35-2.99).

Conclusion: Females with TS have an increased risk of being diagnosed with any neurodevelopmental and psychiatric disorder. This warrants extensive assessment of intellectual and cognitive functions from early ages and increased psychiatric vigilance should be a part of lifelong healthcare for females with TS.

Keywords: Turner syndrome, psychiatric disorder, neurodevelopmental disorder, ADHD, autism spectrum disorder, intellectual disability

22. KEYNOTE: Comorbidities Associated With Down Syndrome Across the Lifespan

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Kings College London

Down syndrome (trisomy 21) is the most common genetic cause of Intellectual disability and associated with a unique pattern of health co-morbidities which may vary across the lifespan, as well as a degree of protection against some conditions. In this talk, I will highlight some of the health risks associated with specific chromosome 21 genes, focusing on infections such as COVID-19 and conditions such as diabetes and Alzheimer's disease. I will highlight both similarities and differences between the comorbidity patterns in childhood and in older adults with Down syndrome, and with the general population.

23: Cross-sectional and Longitudinal Characterization of the Developmental Phenotype in 22q11.2 Duplication

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Background: 22q11.2 duplication is a recurrent copy number variant (CNV), associated with a wide spectrum of physical and neurodevelopmental features and a high rate of familial transmission. In this study, we aim to contribute to the developmental phenotype of this recurrent CNV.

Methods: We conducted a retrospective chart review and analysed the digital medical records of 28 patients with proximal 22q11.2 duplications, focusing on physical, developmental and behavioural features, including longitudinal data in a subgroup (n=11). Additionally, the phenotypes of de novo (n=8) and inherited (n=13) 22q11.2 duplications were compared.

Results: Common physical anomalies include nutritional problems (57%), failure to thrive (33%), transient hearing impairment (52%) and congenital heart defects (33%). Developmental, speech-language and motor delay are common in infancy, while attention (64%), learning (60%) and motor problems (52%) are typically reported at primary school age. Attention-deficit/hyperactivity disorders are diagnosed in 44%. Average full-scale intelligence quotient is in the borderline range (FSIQ 79), with one-third of patients functioning in the borderline range (FSIQ 71-84) and one-fifth of patients having mild intellectual disability (FSIQ 55-70). Longitudinal IQ-data (n=11) indicate that almost two-third of patients have a relative stable cognitive trajectory, whereas one-third show a growing into deficit profile. In patients with de novo duplications, there is a trend of more failure to thrive, while more patients with inherited duplications attend special education.

Conclusion: The present study confirms a wide heterogeneous physical and neurodevelopmental phenotype in patients with proximal 22q11.2 duplications, and provides for the first time longitudinal IQ-data in a subgroup of patients. When children are diagnosed with 22q11.2 duplications prenatally or early in life, healthcare professionals should be aware of an increased risk of nutritional problems, heart defects and hearing problems, and should initiate neurodevelopmental support early in life, given the high risk of developmental delay, learning and attention problems.

Keywords: 22q11.2 duplication, copy number variants, developmental phenotype, de novo versus inherited duplications, Neurodevelopmental Disorders, developmental trajectories

24: Inheritance Matters: Mental Health Risk in Intellectual Disability

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Background: IMAGINE-ID is a national study of behavioural problems and psychiatric risk in children with intellectual disability (ID) of known genetic origin. IMAGINE-ID children have higher rates of mental health and behavioural difficulties than both the general population and children with ID of unknown genetic cause. This study compares the behavioural phenotype of IMAGINE-ID children whose pathogenic variant is inherited and those in whom it is de novo (newly occurring).

Methods: 3,809 children and young people (5 -19 years, 56% male) were recruited via NHS Services and patient support groups. Caregivers completed the Development and Wellbeing Assessment interview, which assesses psychiatric symptomatology and provides DSM-5 classifications based on clinical ratings. The mean age at time of assessment was 9 years. 39% of variants were de novo, 27% were inherited and 34% were of unknown inheritance.

Results: 53% of the cohort met criteria for a mental health or neurodevelopmental disorder. Parents reported significantly more behavioural difficulties, mental health problems and neurodevelopmental disorders in children with an inherited variant compared to those with a de novo variant ($p<.0001$). Children with an inherited variant were more likely to live in more deprived areas ($p<.0001$). Both groups (with or without an inherited variant) were reported to have similar levels of physical disability.

Regression models explored the associations between variant inheritance, socio-economic deprivation and behaviour difficulties. Variant inheritance and socio-economic deprivation were independent predictors of behaviour difficulties ($p<.0001$; $R2 =.11$). The associations remained significant when controlled for age at assessment, sex, age at genetic diagnosis, degree of intellectual disability and level of physical disability.

Conclusion: Earlier identification of variant inheritance together with early intervention and support for children whose parents carry genetic risk may improve their long-term mental health outcomes.

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

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25: The Effect of the Initial UK COVID-19 Lockdown on the Mental Health of Families With and Without a Child With a Rare Disorder

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Background: Families with a child that has a rare neurogenetic disorder (RND) are known to be at higher risk of lower wellbeing. Similarly, social isolation and losing access to support networks is predictive of poor wellbeing. The SARS-COV-2 (COVID-19) pandemic caused a nationwide lockdown in the UK during Spring 2020. For many families with RNDs, shielding was also put into effect until 1st August 2020 due to a higher vulnerability among this population. In this study, we sought to compare the wellbeing of families with RNDs to families without RNDs during the first COVID-19 lockdown.

Methods: In this pre-registered study, using an online survey we collected data on mental health (measured by DASS-21), and parent's perceptions of their child's behaviour (measured by the SDQ) from 122 UK-based families, after exclusion, of children with RNDs (Mage = 8.06, SDage = 3.78). This was compared to matched datapoints in the CoSPACE dataset, a nationwide survey of wellbeing during the pandemic with over 10,000 families.

Results: We found, as hypothesised, that families with a child with an RND had worse mental health scores, as measured by the DASS-21, and that child behaviour had a greater impact. Follow-up analyses were conducted to compare the effect size of this difference to similar effect sizes before the pandemic.

Conclusion: While families across the UK were affected by the Covid-19 pandemic, families of children with an RND experienced greater impact on wellbeing and behaviour. However, the effect on families was not distributed evenly; families that have a child with an RND experienced a greater impact of the pandemic than those without. Examination of longitudinal changes in parental wellbeing and child behaviour over the course of the pandemic will reveal predictors to enable targeting of support, or something similar, to open up further analyses.

Keywords: COVID-19, Coronavirus, Neurogenetic, Intellectual Disability, Developmental Disability, Rare

26: Latent Profiles of Autism Symptoms in Children and Adolescents with Down Syndrome

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Background: Down syndrome (DS) is associated with elevated rates of autism spectrum disorder (ASD). Characterizing heterogeneity in ASD symptom profiles can inform personalized treatment and intervention in this population. To better understand the heterogeneity in ASD symptomatology in DS, profiles of caregiver-reported ASD symptoms in 130 children and adolescents with DS were modelled in this study.
Methods: Participants were recruited through several multi-site research studies on cognition and language in DS. Using the Social Responsiveness Scale-2 (SRS-2), latent profile analysis (LPA) was performed on both the broad composite scores of Social Communication and Interaction and Restricted Interests and Repetitive Behaviour, and then a second LPA was performed that included the four social dimensions of Social Communication, Social Motivation, Social Awareness, and Social Cognition. After identifying the model with the best fit in each analysis, we then conducted auxiliary analyses to examine the role of biomedical risk, IQ, sex, and SRS-2 form (Preschool and School Age) on profile probability scores.
Results: Results showed that a 3-profile model was the best fit for both analyses, both yielding a Low ASD Symptom profile, an Elevated or Mixed ASD Symptom profile, and a High ASD Symptom profile. Auxiliary analyses demonstrated associations between the ASD symptom profile probability scores and IQ, the number of biomedical comorbidities reported, and the SRS-2 form used.
Conclusion: The implications for potential therapeutic approaches to support positive outcomes in individuals with DS are discussed.

Keywords: Down syndrome; social relatedness; autism spectrum disorder; mixture modelling

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27: Autism Symptoms in Children and Adolescents With Fragile X, Angelman Syndrome, Tuberous Sclerosis Complex and Neurofibromatosis Type 1: A Cross-Syndrome Comparison

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Background: Autism spectrum disorder (ASD) is a common comorbid disorder in various genetic syndromes. The aetiology of ASD remains unclear, due to its heterogenic genetic origin and the heterogeneity in symptoms across individuals. This study aims to compare ASD symptomatology in syndromes with a known genetic origin, in order to reveal syndrome specific vulnerabilities that may serve as targets for early intervention and provide insight into the genetic pathways that underlie ASD.

Methods: We assessed ASD symptom severity in four groups of children/adolescents (aged 2-26 years) with syndromes that have high ASD comorbidity: Fragile X Syndrome (FXS, n=53), Angelman Syndrome (AS, n=74), Neurofibromatosis Type 1 (NF1, n=254) and Tuberous Sclerosis Complex (TSC, n=97), using the Autism Diagnostic Observation Schedule (ADOS). Assessments were part of routine clinical care and performed in all children seen at the ENCORE expertise centre in Rotterdam, the Netherlands. We compared the groups on ADOS calibrated severity scores (CSS) and subscale scores using a Kruskal-Wallis test.

Results: Total CSS scores and the percentage ADOS ASD classifications were highest for the FXS-group and lowest for the NF1-group (FXS: 81%, TSC: 51%, AS: 59%, NF1: 14%). When including individuals with an ASD classification only, overall ASD severity was higher in the FXS and TSC groups than in the AS-group. In-depth subscale analyses revealed that the AS-group showed a relative weakness in the creativity/play subscale (highest of all groups) and the reciprocal social interaction subscale (higher than NF1). NF1 showed a relative strength on the restricted interests and repetitive behaviour scale (lowest of all groups).

Conclusion: Comparing the groups at subscale level revealed syndrome-specific strengths and weaknesses that would have gone unnoticed by looking solely at classifications or summary calibrated severity scores. Our findings underline the relevance of comparing ASD symptoms across syndromes and highlight the need for syndrome-specific ASD interventions.

Keywords: Fragile X Syndrome, Angelman Syndrome, Tuberous Sclerosis Complex, Neurofibromatosis Type 1, Autism Spectrum Disorder, ADOS

28: Behavioural and Emotional Characteristics in Children With Bardet-Biedl Syndrome: A Cross Group Comparison

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Introduction: Bardet-Biedl syndrome (BBS) affects 1 in 100,000 individuals and is associated with intellectual disability and progressive sight loss. A number of clinically relevant behavioural and emotional characteristics have been documented in BBS including repetitive behaviour, low mood and anxiety. However, existing research is limited by the absence of appropriate comparison groups. This study examined the behavioural and emotional profile of children with BBS using a cross group comparison approach.

Methods: Parents/caregivers of 17 children with BBS (52.9% male; M_{age} = 9.82; range: 4-15 years) completed measures of autism characteristics, behaviours that challenge, mood and overactivity. Scores on these measures for the BBS group were compared with scores obtained from matched comparison groups of children with Autism Spectrum Disorder (ASD) and children of typical development.

Results: A high proportion of children with BBS (67%) met cut-off on a screening measure of autism characteristics. Children with BBS had significantly elevated total scores for autism characteristics compared to TD children ($U = 23$, $p < .001$), but lower scores than children with ASD ($U = 34.5$, $p < .001$). Children with BBS had greater difficulty with reciprocal social interaction and communication compared to restricted, repetitive and stereotyped behaviours. The BBS group showed more indicators of low mood ($U = 77.5$, $p < .020$), and similar levels of impulsivity, compared to children with ASD. There was a positive trend between greater sight loss and autism characteristics but this did not reach significance.

Conclusion: ASD characteristics are prevalent in BBS and could be indicative of an atypical autism profile. Children with BBS may benefit from routine assessments of ASD and mood. Further research is needed to confirm how sight loss may be contributing to the profile of behaviour and emotion in BBS.

Keywords: Bardet-Biedl syndrome; autism; emotion; behaviour

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29: Use of Language-Based Routing Items to Improve Parent-Report Measures of Social Communication

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Background: Tools designed to screen for delays in social-communication often use chronological age-based guidelines for administration and/or interpretation. However, this approach may not be appropriate for children whose developmental levels are significantly lower than their chronological age. The purpose of this study was to determine the utility of parent-reported language milestones for estimating age, with the idea that these items could be used as routing items to estimate overall developmental level on a new, developmentally-based measure of social communication, the Developmental Assessment of Social Communication Ability (DASCA).
Methods: A sample of 823 parents of neurotypical children aged 1 to 18 years was recruited through a market research firm (Op4G). To determine whether language milestones could be used to predict a child's chronological age, we applied Classification and Regression Trees algorithm to classify binary age groupings (age <48months vs >=48months, when complex speech is typically achieved) from binary language milestones (attained/not attained).
Results: Using two to three language items could classify with 100% accuracy that a child was not older than 48 months: all 188 children who were reported not able to "Use words like 'yesterday' and 'tomorrow' correctly" nor "Re-tell the basic plot of a story or TV show" were under 48 months. Among those who can "Use words like 'yesterday' and 'tomorrow' correctly", children who were not able to "Put verbs in past tense when talking about the past" or "Ask 'When' questions" were under 48 months. However, the classification efficiency for over 48 months was lower, resulting in Cohen's Kappa of 0.61 for the classifier overall.
Conclusion: Technological advances allow for use of novel routing methods in screening and assessment. Our work suggests that parent-reported language milestones are useful for identifying whether a child has a low developmental level, thereby enabling a more developmentally-appropriate selection of questionnaire items.

Keywords: Social communication, measure, developmentally appropriate, language milestones, classification algorithm

30: Sterol and Lipid Analyses Identifies Hypolipidemia and Apolipoprotein Disorders in Autism Associated With Adaptive Functioning Deficits

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Background: An improved understanding of sterol and lipid abnormalities in individuals with autism spectrum disorder (ASD) could lead to an improved understanding of biological mechanisms and personalized treatment approaches.

Methods: We performed cholesterol analyses on blood from 570 subjects with ASD from families with ≥ 2 ASD subjects participating with the Autism Genetic Resource Exchange (AGRE). In subject subsets, we performed HDL-cholesterol, apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), 7dehydrocholesterol (7DHC), lathosterol, desmosterol and sitosterol analyses. Using National Health and Nutrition Examination Survey (NHANES) data, we assigned age-and-sex-adjusted centile values to the levels. We compared ApoA1 and ApoB centiles in 3 groups, age 4 years to 17.9 years, AGRE (n=118), National Institutes of Health (NIH) typically developing control subjects (n=24) and NHANES-survey weighted estimates of the percentage in the typical population (n=157).

Results: We did not identify any individual with Smith-Lemli-Opitz syndrome, lathosterolosis, desmosterolosis or sitosterolemia. Subjects with cholesterol levels less than the 5th centile (<5thCent) had statistically lower levels of 7DHC, lathosterol and desmosterol. ASD subjects had reduced amounts of cholesterol, HDL-cholesterol (HDL), ApoA1 and ApoB, with 30% having either ApoA1 <5thCent (HAL), ApoB levels <5thCent (HBL) or both ApoA1 and ApoB <5thCent (HABL), with 19.9% having patterns similar to hypolipidemic clinical syndromes. Subjects with HDL<5thCent and subjects with HAL had significantly lower Vineland ABC scores than individuals with higher levels. When grouped into the categories of HAL, HBL, HABL and Normal, the ASD subjects had the greatest percentage of HABL and HAL and there was a significant difference in the distribution across the 4 apolipoprotein classifications between the AGRE and NIH groups.

Conclusions: Subjects with abnormally low cholesterol levels had statistically lower levels of 7DHC, lathosterol and desmosterol, indicating that low cholesterol levels were due to reduced cholesterol synthesis. Individuals with ASD with either HDL <5thCent or HAL or HABL have lower adaptive functioning, which points to various potential biological mechanisms due to the roles of HDL and ApoA1 in the brain, and the transport of microRNA via HDL.

Keywords: Sterol, Lipid, Cholesterol, Apolipoprotein, Behaviour, Adaptive function

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31: Genotype Differences in Smith-Magenis Syndrome

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Background: Smith-Magenis syndrome (SMS), a genetic neurodevelopmental disorder associated with major sleep and behavioural disturbances, is estimated to affect up to 1:15.000 live births. SMS is caused by a 17p11.2 deletion or a pathogenic variant in *RAI1*. Previous studies reported a *RAI1* variant in ~10% of the cases. However, this may be an underestimation as at the time of the initial studies, next-generation sequencing technology was not available. Also, the knowledge on genotype-phenotype correlations is scarce.

Method: In order to assess the proportion caused by *RAI1* variants and the effect of genotype on intellectual and behavioural phenotypes, we conducted a retrospective chart review. We reviewed clinical records from patients with a molecular diagnosis of SMS, ascertained through a Dutch SMS specialty clinic. We systematically collected data on demographic variables, genetics, severity of intellectual disability (ID) and behavioural problems. Data on behaviour were obtained with the Child Behaviour Checklist (CBCL).

Results: A total of 66 individuals had data on ID (n=53) and/or CBCL (n=39). Forty-seven individuals (71%) had a 17p11.2 deletion and 19 (29%) a pathogenic *RAI1* variant. The proportion of individuals with a more significant ID was higher (p=0.01) and median full-scale IQ scores were lower (56.0 vs 73.5, p=0.001) in the 17p11.2 deletion group. Median CBCL-scores were higher in the *RAI1* group for: somatic complaints (68.0 vs 57.0, p=0.000), internalizing behaviour (66.0 vs 55.0, p=0.002), withdrawal/depression (69.5 vs 55.0, p=0.02), and total scores (73.5 vs 66.0, p=0.02). Somatic complaints and internalizing behaviour survived correction for multiple comparisons.

Conclusion: The results suggest that: 1) the proportion of patients with a pathogenic *RAI1* variant is higher than reported in previous studies, and 2) the severity of ID is more severe while specific behavioural problems are less severe in individuals with a 17p11.2 deletion compared to those with a pathogenic *RAI1* variant.

Keywords: Smith-Magenis syndrome, 17p11.2 deletion, RAI1 mutation, intellectual disability, behavioural problems, rare disorders

32. KEYNOTE: Targeted Treatments for Fragile X Syndrome: Lessons and Progress

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Rush University Medical Center

Fragile X syndrome (FXS), as a monogenic cause of intellectual disability (ID) and autism spectrum disorder (ASD), has been one of the first neurodevelopmental disorders in which molecular and neuronal mechanisms of disease have been identified, leading to the concept of targeting the underlying disease to reverse symptoms. Despite extensive molecular, cellular and animal model data supporting disease pathway-targeted treatments in FXS, initial clinical trials that were designed based on FDA precedents failed to show benefit for behaviour in adults and adolescents with FXS. Rethinking of translational models and drug development strategies based on this experience revealed gaps in understanding of the optimal age for treatment, trial designs, and outcome measures and biomarkers that assay core aspects of the disease. Much work has been done to address these gaps including development and validation of improved outcome measures such as expressive language sampling, the NIH Toolbox cognitive battery, individualized caregiver report measures in key problem domains in FXS, and biomarkers including eye tracking and EEG with event-related potentials. More recent improved trial designs and early development programs have incorporated better ways to control for placebo response, early PK/PD studies to identify signal, earlier studies in young children and measurement of drug effects on learning in the setting of an intensive learning intervention. These novel trial designs and improved outcome measures are expected to better demonstrate disease modification, with learning and functional improvements. Lessons learned in FXS trials can inform design of trials of targeted treatments for other single gene models of ID/ASD, and for idiopathic ASD.

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33: Global Methylation Profiling in Children With Autism Spectrum Disorder and in Children With Fragile X Syndrome

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Background: Autism spectrum disorders (ASD) is an early onset, developmental disorder with a reported incidence of 1 in 59 people. Among the monogenic causes of ASD, Fragile X syndrome (FXS) that is characterized by a CGG trinucleotide expansion > 200 repeats in the 5'UTR of the *FMR1* gene accounts for 2-4% of ASD cases and 60% of individuals with FXS present with autism. Epigenetic changes, specifically DNA methylation plays a significant role in the pathogenesis of both disorders.

Methods: In this study, we determined the global DNA methylation profiles derived from 57 age-matched male participants (2-6 years old) including 23 subjects with ASD, 23 subjects with FXS with ASD (FXSA) and 11 typical developing (TD) children. Human Methylation EPIC Bead Chips, including 850,000 CpG sites throughout the genome, were used.

Results: Pairwise comparison of three groups, using adjusted p-value less than 0.05, identified significant differential methylated CpG sites (DMs) and a distinct methylation profile in the ASD, FXSA and TD groups. About 40-60% of the significant DMs in each comparison group. Functional enrichment analysis of DMs in within the genes using MethylGSA confirmed dysregulation in several pathways, including immune signaling, Rho GTPase signaling, PI3K/AKT signaling and oxidative phosphorylation in ASD and FXSA. mRNA expression levels measured in a subset of genes lined up with the differential methylation status in two genes: *C11ORF31* and *NF2*. Of these, a significant difference in NF2 expression levels was also confirmed at protein level.

Conclusion: Thus, 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 to develop an improved diagnostic classification of children with ASD and FXSA.

Keywords: Autism spectrum disorders, Fragile X syndrome, Global methylation, neurodevelopment disorder, epigenetics

34: Metabolomic Biomarkers are Associated with Area of the Pons in Fragile X Premutation Carriers at Risk for Developing FXTAS

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Background: Fragile X-associated tremor/ataxia syndrome (FXTAS) is a late adult-onset neurodegenerative disorder that affects movement and cognition in carriers of premutation allele (55–200 CGG repeats; PM) in the fragile X mental retardation (*FMR1*) gene. It is currently unknown how the observed brain changes are associated with metabolic signatures in individuals who develop the disorder over time.

Methods: The correlation between longitudinal changes in brain (area of the pons, midbrain, and MCP width) and expression level of metabolic biomarkers of early diagnosis and progression of FXTAS assessed in PM who, as part of an ongoing longitudinal study, emerged into two categories. First who developed symptoms of FXTAS (converters, CON) at subsequent visits and second who did not meet the criteria of diagnosis (non-converters, NCON) and were compared to age-matched healthy controls (HC). We assessed CGG repeat allele size by Southern Blot and PCR analysis. Magnetic Resonance Imaging (MRIs) acquisition was obtained on a 3T Siemens Trio scanner and metabolomic profile was obtained by ultra-performance liquid chromatography, accurate mass spectrometer, and an Orbitrap mass analyser.

Results: Our findings indicate that differential metabolite levels are linked with the area of the pons between HC and PM groups. More specifically, we observed significant association of ceramides and mannonate metabolites with decreased area of the pons, both at visit 1 (V1) and visit 2 (V2) only in the CON as compared to the NCON group suggesting their potential role in the development of the disorder. Besides, we found significant correlation of these metabolic signatures with the FXTAS stage at V2 indicating their contribution to the progression and pathogenesis of FXTAS.

Conclusion: These metabolites as part of lipid and sphingolipid lipids pathways provide evidence of the role their dysregulation plays in the development of FXTAS and inform us as potential targets for personalized therapeutic development.

Keywords: Fragile X-associated tremor/ataxia syndrome, area of the pons, metabolic biomarkers, brain measures, lipids

35: A Pivotal Study of ZYN002 Cannabidiol (CBD) Transdermal Gel in Children and Adolescents With Fragile X Syndrome [CONNECT-FX (ZYN2-CL-016)]

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Background: ZYN002 is a pharmaceutically manufactured transdermal cannabidiol gel. CONNECT-FX was a randomised, double-blind, placebo-controlled study to evaluate efficacy and safety of ZYN002 in patients 3 to 17 years with full mutation fragile X syndrome (FXS). Silencing of the FMR1 gene in now believed to require complete or near complete methylation of the gene. Patients without silencing of the gene or significant mosaicism may represent a different population with higher levels of FMRP and perhaps mRNA.

Methods: Patients were randomized to ZYN002 or placebo for 12 weeks. The primary endpoint was change from baseline in the Aberrant Behavior Checklist–Community FXS Specific (ABC–CFXS) Social Avoidance subscale. Key secondary endpoints included change from baseline in the ABC–CFXS Irritability and Socially Unresponsive/Lethargic subscales and Clinical Global Impression, Improvement (CGI-I). A pre-planned ad hoc analysis was conducted in patients with ≥90% methylation of the FMR1 gene. Safety assessments included adverse events, laboratories, and electrocardiograms.

Results: 212 patients were randomised. Mean age was 9.7 years; 75% were male. Improvements in ABC-CFXS Social Avoidance, Irritability, and Socially Unresponsive/Lethargic scores and the CGI-I, while greater for ZYN002, were not significant in the overall group. Patients with ≥90% methylation (n=169) showed a significant improvement in ABC-CFXS Social Avoidance (p=0.020) and significantly more patients had a clinically meaningful change in Social Avoidance (OR 2.04, P=.031) and Irritability (OR 2.17, P=.036). ZYN002 was well tolerated. Adverse events were mild to moderate severity; application site pain was the most common treatment-related event (placebo 1%; ZYN002 6.4%). No serious or severe events, nor other relevant abnormalities occurred.

Conclusion: ZYN002 was well tolerated and demonstrated significant improvement in behavioural symptoms of FXS in patients with ≥90% methylation of the FMR1 gene, representing a biological population within FXS most likely to have silencing of the FMR1 gene.

Keywords: Fragile X, Behaviours, FMRP, Cannabidiol

Abstracts for Poster Presentation

(in order of presentation)

POSTER 1: Sleep Management in Smith-Magenis Syndrome: A Qualitative Analysis of Caregiver and Professional Considerations

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Background: Smith-Magenis syndrome (SMS; OMIM #182290) is associated with mutation or deletion to the RAI1 gene on chromosome 17p11.2. Sleep problems are highly prevalent in SMS, characterised by frequent nocturnal wakings, early morning waking, reduced total sleep time, and daytime sleepiness. As a result, stress and sleep deprivation are reported by parents and caregivers. The complex behavioural phenotype in SMS (preference for adult attention, self-injury, aggression, impulsivity) also means there are likely consequences to the individual and their family regarding sleep management and safety at night. As these practical implications have not been addressed in the current literature, this study aimed to describe caregiver experiences of SMS sleep management as well as considerations for UK service provision from the perspective of clinicians and professionals.

Methods: Nineteen caregivers of children and adults with SMS participated in face-to-face interviews or focus group sessions held in both England and Scotland to capture differences in safeguarding and educational support legislation across the two countries. Interviews and professional focus groups were also held in England and Scotland with twelve professionals working within the public sector, including: government, education and health. Thematic qualitative analysis of transcripts was performed.

Results: Caregivers discussed aspects relating to sleep hygiene, the use of medication and the overall impact of sleep problems within the family context. Several themes relating to sleep safety at night were highlighted, including the need for adapted sleeping environments such as enclosed beds and stairgates. Professionals highlighted the need for collaborative judgement, individuality of best care practices, safeguarding issues within residential and school settings, and caregiver respite.

Conclusion: Given the complexity of sleep problems and behaviours associated with SMS, a discord between caregiver experiences and professional understanding are additional barriers to service provision and targeted support. Further clarity is needed regarding safeguarding assessment and legislation in SMS.

Keywords: Smith-Magenis syndrome, sleep, safety, behaviour, qualitative analysis

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POSTER 2: The Impact of X- and Y-Chromosome Variations (XXX, XXY, XYY) on Early Social Functioning: Social Attention, Affect Recognition and Autism Spectrum Disorders Symptoms.

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

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

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

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

Keywords: Sex Chromosome Trisomies, social attention, affect recognition, ASD symptoms, young children

POSTER 3: Reading Skills in Adolescents With 47,XXY (Klinefelter Syndrome), Familial Learning Disabilities (FLD), and Hormonal Replacement Therapy (HRT)

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Background: 47,XXY is the most frequently occurring sex chromosome aneuploidy (SCA) and characterized by variable neurodevelopmental phenotypes that are influenced by several factors including hormonal replacement therapy (HRT) and a history of familial learning disabilities (FLD). Past research has demonstrated that young children with 47,XXY and FLD had significantly reduced reading skills. This study investigated whether these neurodevelopmental differences responded to neurobiological treatment in adolescents with 47,XXY.

Methods: Thirty-five prenatally diagnosed adolescents with 47,XXY (CA: 176 months) were treated with HRT based on their endocrinologist's assessment. They completed neurodevelopmental assessments including the Woodcock Reading Mastery Test, 3rd Edition (WRMT-III). For analysis, the males were segregated into two groups: no-FLD (N=15) and FLD (N=20). Two-tailed t-tests were completed to assess the differences between the two groups.

Results: The no-FLD group had significantly elevated scores on the Word, Passage, Reading, and Listening Comprehension subtests (p=0.0001, p=0.016, p=0.0006, and p=0.043, respectively). However, both groups performed at least average on these subtests with the FLD group scoring 105.63, 108.47, 107.58, and 108.95, respectively. Additionally, the no-FLD group scored significantly better on the Total Reading cluster with a mean score of 119.87 compared to a mean score of 105.79 in the FLD group (p=0.0006).

Conclusion: Males with a positive history of FLD showed reduced scores on several subtests and clusters compared with males in the no-FLD group, consistent with previous findings. This study demonstrated that even with neurobiological intervention, the impact of FLD on reading skills persists. However, the FLD group exhibited average to high-average scores compared to above average scores in the no-FLD group, suggesting HRT may sufficiently mitigate a history of FLD in adolescents with 47,XXY commensurate with neurotypical individuals. Further research is warranted to identify other neurodevelopmental aspects that may be impacted by FLD and whether HRT may improve those aspects.

Keywords: 47,XXY, family learning disabilities, hormonal replacement therapy, reading, sex chromosome aneuploidy

POSTER 4: A Cross-Cultural Examination of the Transdiagnostic Pathways of Emotional Outbursts

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Background: The behavioural phenotypes across several genetic syndromes comprise of emotional outbursts, which can negatively impact the well-being of individuals and their families. There is large within-syndrome variability in terms of the setting events and antecedents associated with outbursts, but the overall repertoire of contexts is similar across syndromes. Therefore, the aetiology of emotional outbursts may involve multiple transdiagnostic pathways that describe distinct emotional and cognitive differences, which determine the contexts in which outbursts occur. This study aimed to identify these pathways transdiagnostically in two culturally distinct samples.

Methods: Caregivers of young people (6-25 years) with genetic syndromes or other neurodevelopmental disorders completed the English or Brazilian Portuguese version of the Emotional Outburst Questionnaire (n=268 and 353, respectively). Potential pathways were identified by examining the patterns of setting events and antecedents related to emotional outbursts through factor and cluster analyses within each sample.

Results: Six factors relating to the contexts of outbursts demonstrated strong measurement invariance across the two versions of the questionnaire. Responses within each sample were classified into three clusters using these factors. The three clusters identified in the English responses were characterised by increased likelihood of outbursts: 1) across all contexts; 2) in safe settings; 3) in unsafe settings. The first two of these clusters emerged from the Brazilian sample, but an additional new cluster was identified and will be further characterised.

Conclusion: The potential pathways based on the English responses may relate to 1) sensory processing difficulties; 2) masking of emotions in unsafe environments; 3) differences in the perception of unsafety. This framework details a transdiagnostic and cross-cultural account of the aetiology of outbursts. Whilst certain genetic syndromes may predispose individuals to outbursts, these pathways may determine how outbursts ultimately manifest. Therefore, characterising the unique differences of each pathway may facilitate the development of pathway-specific interventions.

Keywords: Emotional outburst, temper outburst, neurodevelopmental disorder, challenging behaviour

POSTER 5: How Healthy Are Children With Disability Attending Schools for Specific Purposes in Sydney, Australia?

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Background: Adults with intellectual disability (ID) face far greater morbidity and mortality than the general population. Multi-morbidity and risk factors for chronic illness in this population develop in childhood. Data on the health status of children with ID in Australia is limited. The aim of this study was to describe the health of children with a moderate to severe intellectual disability attending Schools for Specific Purposes (SSPs) in South Eastern Sydney to inform service development.

Methods: Retrospective review of medical records of 116 children attending clinics run within SSPs in South Eastern Sydney. Extracted data included: medical comorbidity, behavioural difficulties, regular medications and monitoring of side effects, health surveillance and health service utilisation.

Results: Three quarters of students with ID attending a SSPs had at least one co-morbid physical health diagnosis. Twenty-six per cent of children had more than 3 comorbid physical health diagnoses. Ninety-two percent of students had behaviour difficulties and 34% were prescribed psychotropic medications.

Conclusion: Our study demonstrated high levels of poor physical and mental health in a population of children with moderate to severe ID attending SSPs. This supports that premise that the pattern of poor adult health and early morbidity in people with intellectual disability is established in childhood and provides paediatric services with an opportunity to change these outcomes.

Keywords: Intellectual Disability, Physical Health, Mental Health, Children

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POSTER 6: Prevalence of Anxiety Symptomatology and Diagnosis in Genetic Syndromes: a Systematic Review and Meta-Analysis

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Background: Individuals with genetic syndromes associated with intellectual disability (ID) are at increased risk of experiencing anxiety. Comparing prevalence estimates of anxiety will allow the identification of at-risk groups and inform causal pathways of anxiety. No known study has explored estimates of anxiety symptomatology and diagnosis, including specific anxiety profiles, across groups whilst accounting for methodological quality of studies. This systematic review and meta-analysis aimed to fill this gap in the literature.

Methods: The current study was completed according to PRISMA guidelines; methodology and analysis plans were registered and documented in a protocol prior to completion of the review (CRD42019123561). Searches were completed on Web of Science, Ovid PsycINFO, Ovid Embase and CINAHL Plus with no restriction on year of publication. Data from 83 papers, involving a pooled sample of 13,708 participants across eight genetic syndromes were synthesised using a random effects model. Included studies were evaluated against quality rating criteria developed specifically for exploring prevalence data across genetic syndromes associated with ID.

Results: Anxiety prevalence ranged from 9% (95% CI: 4-14) in Down syndrome to 73% in Rett syndrome (95% CI: 70-77). Findings also indicated the presence of specific anxiety profiles across groups. Anxiety prevalence across genetic syndromes was higher than for estimates for heterogenous ID and general population groups.

Conclusion: Substantial variability in the prevalence of anxiety and specific anxiety profiles between syndromes identified groups at higher risk than others. This study highlights the importance of identifying high-risk groups and exploring syndrome associated causal pathways of anxiety, allowing us to refine models of risk, identify divergent profiles and promote early intervention. Further research is needed to characterise difference in presentation and profile of anxiety, and to explore the role of genetic factors and gene-disorder-phenotype-environment interactions within and across genetic syndromes.

Keywords: Anxiety, genetic syndromes, intellectual disability, prevalence, review, meta-analysis

POSTER 7: The Case for Person-Ability Scores as Outcomes in Rare Genetic Disorder Clinical Trials

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Background: It is a curious fact that the core impairments of intellectual disability (ID)—cognitive ability and adaptive behavior—are not routinely used as clinical trial outcomes in studies of rare genetic disorders, in which ID is often the predominate phenotype. One explanation is the ID-specific psychometric profile of norm-referenced scores: they are often not sensitive to change, and their reliability is compromised at low values. An alternative to norm-referenced scoring, the person ability score, is designed to assess change, but they have gone unused in neurodevelopmental disability research. Here we summarize the results of applied and simulation studies in which we compared the norm-referenced and person ability scores as clinical trial outcomes.

Methods: In study 1, we compared the observed change in norm-referenced and ability scores from the Differential Abilities Scales in a natural history study of autism spectrum disorder. In study 2, we simulated a series of randomized controlled trials to determine which design factors were associated with a particular advantage of Vineland Adaptive Behavior Scales ability scores over norm-referenced scores.

Results: In the observed data, the pre/post effect sizes were larger for ability scores than for norm-referenced scores, which were sometimes negative (reflecting slower-than-expected development, rather than a regression). The simulation data indicated that true effect size recovery was better for the ability score than the norm-referenced score, and that while the power of norm-referenced scores was impacted by all design factors, the power of the ability score was influenced only by sample size. While type I error rate was generally well-controlled by both scores, only the norm-referenced scores exhibited fatal floor effects.

Conclusion: Outcomes which are sensitive to change are urgently needed for clinical trials of mechanism-modifying treatments for genetic conditions, and our work supports the ability score as a useful alternative to the norm-referenced score.

Keywords: Ability scores, outcome measures, floor effects, psychometrics, intellectual disability, clinical trials

POSTER 8: An Investigation of the Effect of Hormonal Therapy on Behavioral Outcomes in 47,XXY (Klinefelter syndrome)

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Background: 47,XXY (Klinefelter syndrome) is the most common X and Y chromosomal variation (1:660) that presents with androgen deficiencies and often anxiety, ADHD, and executive dysfunction. Testosterone treatments have been associated with improved behavioral outcomes. This study investigates the effects of early hormonal treatment (EHT) and hormonal booster therapy (HBT) on behavioral phenotypes in boys prenatally diagnosed with 47,XXY.

Methods: The parents of eighty prenatally diagnosed children with 47,XXY (M = 114 months) between the ages of 7 and 12 completed the Childhood Behavioral Checklist (CBCL). The cohort was segregated into four groups based on testosterone status: no-T (N = 16), EHT (N = 13), HBT (N = 28), EHT&HBT (N = 23). An analysis of variance (ANOVA) was completed to assess differences between the groups.

Results: There were no significant differences found for demographic variables between the groups. An ANOVA revealed that the EHT&HBT group showed significantly less aggressive behavior on the CBCL than the no-T (p = .0013) and EHT groups (p = .0393). Additionally, the EHT&HBT group showed significantly lower scores for oppositional defiant disorder compared to the no-T (p = .0088) and EHT groups (p = .0316). There were no significant differences for anxiety (p = .180) or ADHD (p = .151) between the groups.

Conclusion: This study expands on the behavioral phenotype of boys with 47,XXY. Interestingly, receiving testosterone treatment, particularly EHT&HBT, was associated with lower aggression and defiance as opposed to participants who received no-T or only EHT. This finding reveals a significant, positive treatment effect of receiving both EHT and HBT on executive functioning and frontal lobe development in this population. This study adds to the growing evidence of improved neurodevelopment in males with 47,XXY that receive neurobiological treatment. Further research is necessary to determine optimal timing and dosage of testosterone administration.

Keywords: 47,XXY, Klinefelter syndrome, behavior, testosterone, hormonal replacement therapy, phenotype

POSTER 9: EEG as a Translational Biomarker and Outcome Measure in Fragile X Syndrome

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Background: Fragile x syndrome (FXS) is a prime candidate for pharmaceutical treatment: It is prevalent, can disrupt quality of life and its genetic origins suggest strong potential for remediation. This has been furthered by findings of strong parallels in animal models of FXS. However, targeted treatments for FXS have frequently failed to show efficacy in clinical testing, despite success at the preclinical stages, highlighting a need for more effective translational outcome measures.

Method: We reviewed the current literature on EEG characteristics in FXS which could serve as translational biomarkers.

Results: Several EEG differences have been observed in FXS, including exaggerated N1 ERP amplitudes, increased baseline gamma power and reduced gamma phase-locking in the sensory cortices. These abnormalities are thought to reflect cortical hyperexcitability resulting from an excitatory (glutamate) and inhibitory (GABAergic) imbalance in FXS, which has been the target of several pharmaceutical remediation studies. EEG differences observed in humans also show similarities to those seen in laboratory models of FXS, which may allow for greater translational equivalence than is currently observed in other outcome measures and better predict clinical success of putative therapeutics. There is some evidence from clinical trials showing that treatment related changes in EEG may be associated with clinical improvements, but these require replication and extension to other medications.

Conclusion: Although the use of EEG characteristics as biomarkers is still in the early phases, and further research is needed to establish its utility in clinical trials, the current research is promising and signals the emergence of an effective translational biomarker.

Keywords: EEG, biomarkers, translation, fragile x syndrome

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POSTER 10: The Developmental Impact of Sex Chromosome Trisomies on Self-Regulation in Young Children: Evidence From Neurocognitive Tests and Daily Life Behaviour

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Background: Sex chromosome trisomies ([SCT], 47,XXX, 47,XXY, 47,XYY) are amongst the most common chromosomal aneuploidies and occur in 1 in 1.000 births. Around 25% of individuals with SCT are at significant risk for neurodevelopmental problems. The early TRIXY childhood study at Leiden University aims to understand the developmental risks of growing up with an extra X or Y chromosome. This abstract will focus on the presentation of study results concerning the developmental impact of SCT on self-regulatory skills, in terms of Attention Deficit-Hyperactivity/Impulsivity (ADHD-)symptomology and emergent executive functioning.

Methods: The sample consisted of 104 children with SCT and 101 population-based controls, between the ages of 1 to 7 years old. Methods included parental-questionnaires (SWAN and BRIEF(-P)) and neurocognitive tasks of both global EF skills (MEFS) and verbal EF skills (NEPSY Verbal Fluency). Executive functioning measures were assessed from 3 years of age.

Results: Children with SCT showed significantly more self-regulatory difficulties than controls, in terms of symptoms of inattention and both general and specific executive functioning deficits. Increasing age was associated with more dysregulation in the SCT group. Executive function problems were more pronounced and broader in older children with SCT (5-to-7-year-olds).

Conclusion: This is the first study to report weaknesses in self-regulation in young children with SCT, as early as toddlerhood. Children with SCT are at increased risk for dysregulation in early childhood with increasing problems with age. Further investigation is needed to investigate the developmental trajectories of young children with SCT and to validate whether a growing into deficit phenomenon is present. Knowledge on the early development is needed to learn more about early risk factors in the development of young children with SCT, to improve clinical care by providing at-risk markers in development to guide early preventive and appropriate interventions.

Keywords: Childhood development, sex chromosome trisomies, genetic syndromes, self-regulation, ADHD, executive function

POSTER 11: Altered Development of Adaptive Behaviour and Sleep Duration in Infants Predicts Emerging Autistic Traits in Tuberous Sclerosis Complex

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Background: Tuberous Sclerosis Complex (TSC) is a genetic disorder characterised by neuropsychiatric comorbidities, including autism spectrum disorder, intellectual disability, sleep and behavioural difficulties. In TSC populations, studies have observed a decline in adaptive functioning, however specific correlates of adaptive behaviour, such as sleep, have not been explored in infant years. Sleep difficulties are often observed in individuals with TSC and autism. Hence, it is key that the interaction between adaptive behaviour and sleep, and their impact on emerging autism in TSC, is better understood.

Methods: The Early Development in Tuberous Sclerosis (EDiTS) Study employed a prospective, longitudinal design to track behaviour, development and sleep in infants aged between 3 and 24 months of age with TSC (N=32), compared to typically developing infants (N=34). Parent-report questionnaires were used to collect data at up to 7 timepoints on infant's adaptive behaviour (Vineland Adaptive Behaviour Scales-II), sleep patterns (Sleep diaries) and emerging autistic traits in toddlerhood (Q-CHAT).

Results: While no group differences were observed up to 8 months old, at 10, 14, 18 and 24 months of age adaptive behaviour scores were significantly lower in infants with TSC compared to typically developing infants, $F(4,17)=5.03$, $p=.007$. Nighttime sleep duration at 10 months was significantly shorter in infants with TSC, however sleep in the first year of life was not associated with later adaptive behaviour scores. At 10 months, adaptive behaviour scores and night-time sleep duration together predicted Q-CHAT scores at 24 months $F(2, 25)=18.89$, $p<.001$, $R2=.60$.

Conclusion: Adaptive behaviour begins to diverge from the second year of life, suggesting slower skill acquisition in infants with TSC. While sleep and adaptive behaviour were not significantly associated, they predict emerging autism traits, which supports interventions targeting these developmental markers to improve neurodevelopmental outcomes for infants with TSC. Further analyses will examine associations with sensory issues.

Keywords: TSC, Development, Autism, Adaptive, Behaviour, Sleep

POSTER 12: Virtual Navigation in Fragile X

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Background: Neuroscientific research utilises Fragile X animals to model Fragile X Syndrome (FXS) and Autism Spectrum Disorder (ASD) to better understand how neurological development shapes manifesting phenotypes. This research, however, lacks sensitive behavioural tasks which accurately measure degrees of impairment in certain behaviours and the neural substrates underpinning them. Developing such tasks for cross-species delivery would dramatically improve our understanding of the progression and variability of FXS and ASD behaviours, and in turn contribute to diagnostic and therapeutic strategies for neurodevelopmental disorders. This study re-adapted a Virtual Reality (VR) task from animal models into a sensitive assay for stratifying optic-flow driven Path Integration (PI) as a navigational ability dependent upon the hippocampus and retrohippocampal and medial entorhinal cortices. Establishing baseline PI abilities in neurotypical individuals is critical to later identify deviations and deficits in FXS and ASD populations.
Methods: 15 neurotypical participants were recruited from Edinburgh and subject to testing. Seated participants wore the VR helmet and propelled their motion through a linear corridor using a joystick. Instructions to correctly stop within hidden target zone on first attempt was provided, and performance was assessed by first stop position, first stop error, and percentage correct trials.
Results: Similarly to findings in animal models, PI ability worsens with increasing distance of the hidden target zone from the starting position. Increased variability in speed on each trial also impaired PI abilities, which reveals that uncertainty of sensory input is a factor shaping PI accuracy. Overall, a general trend of overshooting to undershooting target location was observed with increasing target distance.
Conclusion: Overshooting to undershooting target distance revealed that sensory systems are the main source of error in path integration computations. Comparing performance of neurotypical and FXS individuals will be critical to investigate sensory processing differences and navigational variations between these genetically distinct groups.

Keywords: Virtual Reality, Navigation, Path Integration, Translatability, Neurodevelopmental Disorders

POSTER 13: Perspectives on the COVID-19 Pandemic: Report from Families

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Background: The world has suffered immeasurably during COVID-19, with concomitant behavioral health problems. University of Pennsylvania (UPenn) investigators reported a 1SD increase in COVID-19 worries associated with a 2-fold increase in generalized anxiety, 67% increase in depression, and an escalation of postpartum depression. The G2MH Network sought to understand how stakeholders affected by copy number variations (CNVs), including 22q11.2, were coping.

Methods: The UPenn abbreviated COVID-19 Distress Survey was circulated by 22 advocacy groups, including 22q11.2 organizations, in English and 11 other languages.

Results: 663 people from 29 countries completed the survey. Most respondents were mothers of children with 22q11.2 CNVs. Top worries included: family members acquiring COVID, unknowingly transmitting/personally acquiring COVID, financial pandemic-related burdens, dying from COVID, and currently having COVID. No differences were found, compared with the general population, by region, CNV type, respondent type, timing of the survey, sex or age. However, for those with higher COVID-related worries, a significant effect on health due to care interruption during the pandemic was noted, primarily in the areas of rehabilitative medicine and genetics. In fact, 46% (N=305) of participants receiving hospital-based primary care delayed appointments due to COVID-19 fears. Importantly, 96% of 517 individuals receiving care via telehealth during the pandemic reported a positive experience.

Conclusions: Effects of the COVID-19 pandemic for 22q11.2 conditions were broadly consistent with research results from other patient populations. Long term effects of COVID-19 distress, interruptions to care, and hospital avoidance require further study. Notably, telehealth was viewed as a major positive.

POSTER 14: Cerebellum Structural Development in Individuals With NRXN1 Deletions, a Rare Copy Number Variant Associated With Neurodevelopmental and Neuropsychiatric Disorders.

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Background: Copy number variants (CNVs) can lead to disrupted gene function through deletions or duplications of segments of DNA. NRXN1 deletions are one rare CNV associated with neurodevelopmental disorders (NDDs), including autism spectrum disorders (ASD), intellectual disability, and speech and language delay. NDDs are characterised by cognitive impairments, behavioural difficulties, and atypical brain development. The NRXN1 gene encodes for a presynaptic cell-adhesion molecule important for synaptic function and efficient neurotransmission within the brain. Although widely expressed in the brain, the NRXN1 gene is highly expressed in the cerebellum and frontal lobes. Structural and functional differences in the cerebellum have been observed in NDDs such as ASD. While traditionally linked to motor function, a growing body of evidence has suggested cerebellum involvement in higher order processes, including language, through cortico-cerebellar connections. This study aims to compare cerebellum structure between individuals with NRXN1 deletions and typically developing (TD) controls. We hypothesise that individuals with NRXN1 deletions have altered gene expression in the brain, including the cerebellum, which may impact structural and/or functional development, leading to cognitive and clinical outcomes.

Methods: High resolution T1-weighted anatomical MRI scans were collected in 17 individuals with NRXN1 deletions and 17 age- and gender-matched TD controls (age = 9-53 years), and analysed using SUIT software to isolate cerebellar structures and perform voxel-based morphometry. Comparisons of local grey matter concentration between NRXN1 deletion and control groups will be performed.

Results: Analysis is ongoing, and statistics will include group comparisons, with age and gender as covariates.

Conclusion: NDDs are highly heterogeneous, both phenotypically and etiologically. Characterisation of rare CNVs, such as NRXN1 deletions, provides a unique approach to examine mechanistic causal links to brain development, and cognitive and clinical outcomes. Examination of brain structure in individuals with NRXN1 deletions may identify a structural biomarker for this genetically defined group.

Keywords: Neurodevelopmental disorders, copy number variants, brain structure, brain development, cerebellum, structural biomarker

POSTER 15: Gaze Following in Fragile-X Syndrome and Cornelia de Lange Syndrome

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Introduction: Autism is highly prevalent in Fragile-X (FXS) and Cornelia de Lange (CdLS) syndromes. A distinct profile of autism characteristics is common, indicating there may be differences in the underlying social-cognitive features contributing to the development of autism characteristics in these groups. In this study, we evaluated whether individuals with FXS and CdLS show similar attentional responses to shifts in eye gaze compared to autistic children and neurotypical children (NT). The impact of high vs. low social demand on attentional responses was also evaluated.

Method: Individuals with FXS (N=10; Mage = 11 yrs), CdLS (N=11; Mage =9 yrs), autistic children (N= 22; Mage = 7 years) and NT children (; N=32; Mage = 6 yrs), comparable for receptive language skills participated. Participants were presented with a passive viewing paradigm, similar to that developed by Senju and Csibra (2008). Videos were presented in which a central cue (ball/cartoon face/human face) directed attention towards one of two objects. Spontaneous gaze patterns were recorded using eye-tracking.

Results: Data collection is ongoing. Preliminary analyses indicate that autistic children and those with FXS and CdLS generally paid less attention to all central cues than NT children ($p<.001$). Autistic, FXS and CdLS participants were just as likely as NT children to follow directional cues to look at the target object ($p>.05$). NT children looked longer at the target object following facial gaze cues ($p<.01$), while autistic participants looked longer at the target object following cartoon gaze cues ($p=.02$). Participants with FXS and CdLS responded similarly to all cues ($p>.05$)

Conclusion: Findings indicate that individuals with CdLS and FXS show similar patterns of gaze and gaze following compared to autistic children and these in turn differ from that of NT children. The value attributed to shifts in gaze differs across participant groups and this may differentially impact the development of social-communication skills.

Keywords: Fragile-X syndrome, Cornelia de Lange syndrome, gaze following, Autism, social-cognition, eye tracking

POSTER 16: The Power of 1: Systematic Review and a Study Protocol for N-of-1 Studies in Rare Genetic Neurodevelopmental Disorders

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Background: Millions of people worldwide are affected by one of the nearly 6000 rare genetic neurodevelopmental disorders (RGNDs), often associated with intellectual disability (ID). Interventional research is challenging due to vulnerable, small and heterogeneous patient populations. As randomised controlled trials (RCTs) in large patient groups are often not feasible, N-of-1 studies - randomised, controlled, multiple crossover trials within single patients - may provide a useful alternative. To improve the use of N-of-1 studies in RGNDs, we systematically reviewed the literature and formulated recommendations. In addition, we designed an N-of-1 trial protocol to study the effectiveness of cannabidiol (CBD) on behavioural manifestations in three different RGNDs.
Methods: EMBASE and MEDLINE were searched for N-of-1 studies in RGNDs. Information was recorded on types of interventions, outcome measures, validity, strengths and limitations. An N-of-1 trial protocol was designed to study the effectiveness of CBD in children and adults with Tuberous Sclerosis Complex, Fragile X syndrome and Sanfilippo syndrome.
Results: In the systematic review, twelve N-of-1 studies were identified for drug as well as non-drug interventions. Main strengths were the use of personalised and clinically relevant outcome measures. Limitations included lack of power analyses and the use of ancillary statistical analyses. Generalizability was compromised due to limited use of validated and generalizable outcome measures.
Conclusion: Properly executed N-of-1 studies may provide a powerful, patient-centred alternative to conventional RCTs. Beside the suitability at an individual level, these should pursue the generalization to a population level. To illustrate how such challenges can be overcome, we present an N-of-1 protocol to investigate the effectiveness of CBD on behavioural problems in RGNDs. Recommendations are provided to develop an N-of-1 framework to realize the sorely needed evidence-based interventions in the future, ultimately optimising evidence-based and personalised care.

Keywords: N-of-1, rare disorders, genetic, inborn errors of metabolism, personalised care

POSTER 17: The Profile of Anxiety in Angelman Syndrome

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Background: Anxiety has been clinically and anecdotally reported in Angelman syndrome (AS), but very few empirical studies have described the profile and associated risk factors. This study aims to 1) describe the profile and triggers of anxiety in AS and 2) explore which characteristics may influence anxiety in AS.

Methods: A questionnaire study was conducted with 40 parents/carers of individuals with Angelman syndrome (*mage* = 21.8, SD = 11.4). Measures of anxiety, triggers of anxiety and characteristics associated with anxiety were included and were validated for people with intellectual disability.

Results: The most endorsed triggers of anxiety across individuals with AS were 1) Injections, needles and blood (n= 16, 40%), 2) others being upset or cross with someone else (n = 13, 32.5%) 3) Others being upset or cross with them (n = 12, 30%). A multiple regression analysis was used to explore predictors of anxiety in AS. The model significantly explained variance in scores on the generalised anxiety subscale of the Anxiety Depression and Mood Scale (ADAMS) ($F(5,32) = 12.298$, $p < .001$, adj $R2 = .604$). Out of the five characteristics included in the model, only genetic aetiology (B = -2.450, $p = .020$) and intolerance of uncertainty (B = .170, $p < .001$) significantly predicted ADAMS generalised anxiety subscale scores.

Conclusion: This study highlights that across individuals with Angelman syndrome individuals with a non-deletion aetiology may be more at risk of experiencing anxiety. Additionally, intolerance of uncertainty may contribute to the development and maintenance of anxiety, which aligns with findings across individuals with intellectual disability. However, autism severity did not. These findings have implications for informing prevention and support strategies for individuals with AS experiencing anxiety.

Keywords: Angelman syndrome, anxiety, behavioural phenotype, intellectual disability, intolerance of uncertainty, risk factors

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POSTER 18: Altered Subcortical and Cortical Brain Morphology in Adult Women With 47,XXX: A 7-Tesla Magnetic Resonance Imaging Study

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Background: Triple X syndrome (47,XXX) is a relatively common sex chromosomal aneuploidy characterized by the presence of a supernumerary X chromosome in females and has been associated with a variable cognitive, behavioural and psychiatric phenotype. 47,XXX may serve as a suitable model for studying the effect of genetic architecture on brain morphology. Therefore, we examined subcortical and cortical brain morphology in adult women with 47,XXX.

Methods: Twenty-one women with 47,XXX and 22 age-matched healthy controls were included in this cross-sectional study. Structural T1-weighted images were acquired using a 7-Tesla Magnetic Resonance scanner. Measures of subcortical brain volumes, cortical surface area and thickness, and cortical folding were obtained and compared between the groups. Additionally, we examined potential relationships between brain outcome measures and social functioning and social cognition in 47,XXX.

Results: Compared to controls, 47,XXX subjects showed lower volumes of the thalamus, caudate, putamen, hippocampus, accumbens and pallidum, and larger lateral ventricle volumes. Lower surface area was found in the superior frontal gyrus and superior temporal gyrus in 47,XXX subjects compared to controls. Altered cortical thickness and cortical folding were not present in 47,XXX. Cortical thickness was associated with social cognition in 47,XXX.

Conclusions: Results suggest that a supernumerary X chromosome affects subcortical and lateral ventricle volumes, and cortical surface area in adult women. 47,XXX may serve as a suitable model for studying genetic influences on structural brain morphology in order to understand neurobiological mechanisms underlying cognitive and behavioural impairments.

Keywords: 47,XXX, sex chromosomal aneuploidy, 7T, brain morphology, social functioning, social cognition

POSTER 19: Correlates of Risk for Behaviours That Challenge in SATB2-Associated Syndrome

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Background: SATB2-associated syndrome (SAS) is a multisystem neurodevelopmental disorder caused by alterations to the *special AT-rich sequence-binding protein 2* gene located on chromosome 2. SAS is characterised by moderate to profound intellectual disability, speech delay and palate and teeth anomalies. Behavioural difficulties are a core feature of SAS; however, there is limited research on specific forms of behaviour that challenges (CB), or correlates of risk for CB.

Methods: Eighty-one parents/caregivers of individuals with SAS (53.1% male; M_{age} 10.12 years) completed questionnaires of behaviour, health, emotion, and autism characteristics. SAS individuals were grouped based on the presence or absence of forms of CB: self-injury, aggression, property destruction. Comparative behavioural analyses were conducted to compare questionnaire subscale scores between CB groups. Characteristics that significantly differed between presence/absence groups were entered into hierarchical logistic regression analyses for each form of CB.

Results: High rates of self-injury (42%), aggression (77%), and property destruction (49%) were reported. The comparative behavioural analyses indicated variation in the correlates associated with each form of CB. The hierarchical regression models for each CB were significant (*p*s <.001): self-injury ($\chi^2(5) = 38.46$, $R^2 = .571$); aggression ($\chi^2(4) = 25.12$, $R^2 = .414$); property destruction ($\chi^2(4) = 23.70$, $R^2 = .346$), explaining between 34.6% and 57.1% of the variance. The variables explaining most variance were gastro-oesophageal reflux and social-communicative difficulties for self-injury, impulsivity and compulsivity for aggression, and compulsivity and male gender for property destruction.

Conclusion: There is variability in the correlates of risk for different forms of CB in SAS, highlighting the importance of a high degree of specificity when examining CB. Understanding factors associated with CB may inform interventions in SAS. Regression models only explained a proportion of the variance for each CB, indicating that other characteristics (e.g., poor sleep) may be implicated.

Keywords: SATB2-associated syndrome, challenging behaviour, self-injurious behaviour, aggressive behaviour, property destruction

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POSTER 20: Identifying the Distinguishing Characteristics of Emotional Outburst Severity

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Background: Emotional outbursts are displays of intense, challenging behaviour and are prevalent in individuals with neurodevelopmental disorders. Outbursts present a danger to individuals and their carers and are cited as reasons for referral to mental health services. The severity of outbursts experienced by individuals correlates with the negative impact on parental mental health. However, it is currently unclear how the characteristics of outbursts may determine the severity of the phenomena.

Methods: Carers (n=214) of individuals aged between 6 and 25 and experiencing outbursts at least once a month (including young people with several genetic syndromes) completed the Emotional Outburst Questionnaire. A subset of questionnaire items were used to compare behaviours seen in most severe and least severe outbursts through quantitative and content analyses.

Results: Signs of physiological arousal and all forms of aggression were reported significantly more in most severe outbursts compared to least severe outbursts. Least severe outbursts were observed more frequently, but most severe outbursts were noted to have a longer duration, be at a higher intensity, and have a longer recovery time. Additionally, associations were found between reduced eye contact and most severe outbursts, as well as expression of suicidal ideation and most severe outbursts. No behaviours were significantly associated with least severe outbursts.

Conclusion: Certain behaviours, namely forms of aggression and physiological arousal, are associated with most severe outbursts. Findings of this study may justify work examining cross-syndrome differences in behaviours associated with most severe and least severe outbursts. Therefore, identification of the distinguishing behavioural characteristics of the most severe outbursts may inform targeted interventions aiming to reduce the severity and associated impact of outbursts. Additionally, identification of characteristics linked to most severe and least severe outbursts could aid in measurement of outburst severity, which would allow for more reliable and valid studies on outburst interventions.

Keywords: Emotional outburst, temper outburst, neurodevelopmental disorder, challenging behaviour

POSTER 21: A Systematic Methods Overview of Emotion Regulation Strategies Used In and Amongst Children and Young People

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Background: Emotion regulation difficulties are relevant to the behavioural phenotypes of many genetic neurodevelopmental disorders. For example, emotional outbursts are prevalent behavioural phenotypic components in Prader-Willi, Smith Magenis and Lowe syndromes. Lack of consistency in how emotion regulation is defined and therefore approached in a training context has limited prior interventions. Effective training requires a comprehensive approach to defining emotion regulation and associated strategies that can be trained. Here, we conducted a systematic methods review of emotion regulation in young people to inform such intervention development.

Method: We systematically identified and synthesised emotion regulation strategies and interventions used in and amongst children and young people. In line with systematic methods reviewing procedures, emphasis was placed on broad searching of relevant literature. An initial hand search used recommendations from practising clinicians to identify relevant psychotherapeutic manuals and prior reviews on emotion regulation. Emotion regulation strategies were identified and clustered thematically. This search was supplemented by a systematic search of PsycInfo, conducted in line with PRISMA guidelines, to check the comprehensive scope of the generated clusters.

Results: The primary outcome will be a cluster analysis of common emotion regulation strategies and targets in young people. Emerging clusters are categorised as 'personal', 'interpersonal' or both. Most clusters, such as acceptance, altering thoughts, and behavioural change are used in both contexts. Others are limited to either personal or interpersonal contexts. Clusters generated will be used to inform a digital intervention targeted at improving emotion regulation in adolescents.

Conclusion: Emotion regulation strategies may relate to transdiagnostic difficulties seen in the behavioural phenotypes of many genetic neurodevelopmental disorders. Thus, if ongoing research on emotion functioning in genetic syndrome identifies alterations in emotion regulation strategy use as part of certain behavioural phenotypes, this review will be useful in the development of interventions and preventative measures.

Keywords: Emotion regulation, systematic methods overview, emotion regulation intervention, intellectual disability, adolescence, behavioural phenotypes

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POSTER 22: "The Genetic Puzzle": A Psychoeducational Tool to Facilitate and Support Communication Around a Copy Number Variation (CNV) in the Family

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Background: In families affected by genetic conditions such as Copy Number Variations impacting neurodevelopment (CNV-NDD) (22q11 DS/dup; 16p11.2 DS/Dup, ……), parents face many challenges: the impact of the CNV (for their child) in terms of outcome (medical and developmental), the necessary treatments, but also the need of explaining the diagnosis to their children (affected child and siblings). Many parents struggle to know and decide when, how and what to tell.

Method: In order to facilitate communication around 22q11 DS in the family and to provide support for parents in the process of diagnosis disclosure, we developed in 2018 a psycho-educational tool (for parents, children affected by a CNV and their siblings): "the genetic puzzle".

Results: Since 2019, we are using this psycho-educational tool in the genetic clinic of the University Hospital Leuven with families with a child with a CNV, and we developed a website: www.geneticpuzzle.eu. Both parents, children and siblings report that their understanding of the CNV has increased, and that the communication around it within the family has improved. Main advantages of the tool that families report are: (a) the tool can be used in a flexible way, (b) information on the CNV can be shared and discussed accordingly to developmental stage and clinical presentation, and (c) with respect to the needs of all family members.

Conclusion: There is a need for families with a child with a CNV to have access to appropriate psychoeducation that answers their questions and improves their understanding. In this presentation we will present this tool and our clinical experience.

Keywords: Genetic puzzle, CNV, psycho-education, communication

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POSTER 23: A Study of Case Series: The Impact of a Parental Training Program on Behavioral Problems in Children and Adolescents with PWS and Their Caregivers

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Background: Prader-Willi Syndrome (PWS) is a genetic disorder caused by the lack of expression of the genes from the paternal chromosome region 15q11-13, and the symptoms of the disorder are hypotony, hyporeflexia, hyperfagia, obesity, behavioral problems and intellectual disability. Despite the neurobiological factors involved in the pattern of hyperfagia and emotional and behavioral problems, parent training is still considered one of the most efective intervention options for children and adolescents with the syndrome. Proper parenting practices can reduce parental mental health problems, as well as improvement in child behavioral problems. The study aimed to developed, apply and assess the efficiency of a parent training program for behavioral management of children and adolescents with PWS.

Methods: The sample was composed of five children/adolescents with PWS, ages 6 to 16 years old. Instruments were: a) Questionnaire for assessing the knowledge of mothers about the syndrome; b) Child Behavior Checklist for Ages 6-18 (CBCL/6-18); c) Adult Self-Report for Ages 18-59; d) Parenting Styles Inventory – maternal and paternal educational practices. The assessments were pre-intervention, during intervention, post-intervention and follow-up. Parental intervention was based on description and characterization of the syndrome and skills development, such as problem solving, expanding the support network, improving interpersonal communication, use of positive reinforcement and positive monitoring and less use of punishment.

Results: The results indicate that the children/adolescents group presented expressive improvement in emotional and behavioral aspects, but no improvement in socialization indicators. Mothers adopted parenting educational practices based on positive monitoring, reduced or eliminated the use of risk practices and acknowledged harm effects of the use of negative parenting practices with their children.

Conclusions: The mothers learned to identify and manage several factors that impaired physical health and behavior problems of their children, and children presented expressive improvement in emotional and behavioral complaints.

Keywords: Prader-Willi Syndrome, children, adolescent, behavioral problems, parental, training program

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POSTER 24: Rare Causes of Primary Amenorrhea and Gender Identity Development

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Background: Primary amenorrhea is a complex condition that often requires a genetic diagnosis. We refer about a case of X tetrasomy (48,XXXX) and a case of gonadal dysgenesia 46, XX in two women now in adult age (48 yrs and 23 yrs respectively) who were diagnosed because of pubertal delay.

Methods: Clinical and neurological, psychometric (WAIS-R, Vineland, SCQ, BEM, MMPI-2) and neuroimaging evaluation.

Results: Case 1 - 48 yrs. Single born, normal psychomotor development, no speech delay, recurrent infections during childhood. No menarche until 15 yrs. Following endocrinological and genetic evaluation, diagnosis of X tetrasomy (karyotype on lymphocytes and skin biopsy) and substitutive treatment since then. Non-Hogkin B cell Lymphoma at 33 yrs. Tomboysm in infancy and adolescence, bisexual orientation in adult life. H 180 cm (> 95%ile), dysmorphic features and global motor impairment. Total IQ 67, VIQ 68, PIQ 72, Vineland lowest scores for socialization scale, SCQ normal, BEM: androgynous gender identity. MRI: mild frontal atrophy and microvascular gliosis

Case 2 - 23 yrs. Single born, normal psychomotor development. No menarche at 17 yrs, late diagnosis of hypogonadotropic hypogonadism, in ovaric dysgenesia 46 XX. Substitutive treatment since 18yrs of age. CGH array and NGS: normal results. Normal intellectual development. University student. Female sexual orientation, anxiety and mood disorders, linked to defective physical phenotype (breast underdevelopment). For this reason, she underwent mastoplastic at 22 yrs. H 174 cm (> 85% ile), normal neurological evaluation. Total IQ 111 VIQ 113, PIQ 106; MMPI-2: profile within the normal range; SCQ: normal; BEM: female gender identity. MRI: functional pituitary hyperplasia.

Conclusion: Both patients presented a difficult approach to their gender identity: in the Case 1 tomboysm during infancy and adolescence and bisexual orientation in adult life. Case 2 had a female sexual orientation, but she underwent a mastoplastic surgery, to repair a poor breast development and to confirm her the female identity.

Keywords: Primary amenorrhea, X tetrasomy, gonadal dysgenesia 46XX

POSTER 25: Parkinsonism in Individuals With Genetic Neurodevelopmental Disorders: A Systematic Review

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Background: While brain disorders are traditionally dichotomized into neurodevelopmental and neurodegenerative disorders, there is increasing evidence of an overlap in its genetic determinants. With advances in clinical genetic testing for neurologic disease, the number of genetic neurodevelopmental disorders (GNDs) associated with parkinsonism is growing fast. Recognition of these GNDs could improve disease-specific medical care and help in our understanding of pathophysiological mechanisms. We aim to provide an overview of GNDs that are associated with parkinsonism, substantiated with the best available evidence on genotype, phenotype and proposed pathophysiology.
Methods: We conducted a systematic literature review, and searched PubMed and EMBASE on May 31, 2020. General search terms for GNDs and a list of GNDs as per the Human Phenotype Ontology, were combined with terms for parkinsonism. Study characteristics and descriptive data on GNDs and parkinsonism were extracted using a modified version of the Cochrane Consumers and Communication Review Group's (CCCRG) Data Extraction Template. The review was registered in PROSPERO (number CRD42020191035).
Results: Our literature search yielded 181 articles reporting on 63 different GNDs and co-morbid parkinsonism in 379 individuals. The five most reported GNDs from most to least frequent were: 22q11.2 deletion syndrome, beta-propeller protein-associated neurodegeneration, Down syndrome, cerebrotendinous xanthomatosis and Rett syndrome. Overall, the median age of motor-onset was <30 years and most individuals responded well to anti-dopaminergic medication. Neuropathology results were reported in 11 articles.
Conclusions: Many GNDs have been associated with parkinsonism. Therefore, clinicians who take care of patients with GNDs included in this study should be aware of a possible increased risk of parkinsonism. Also, a history of a neurodevelopmental disorder could prompt clinicians to consider genetic testing. Further recognition of parkinsonism in GNDs could provide better insights into the mechanisms causing parkinsonism and contribute to the development of disease-modifying treatments.

Keywords: Genetic, neurodevelopmental disorders, neurodegenerative disorders, parkinsonism, Parkinson's disease

POSTER 26: Patterns of Delay in Early Gross Motor and Expressive Language Milestone Attainment in Probands with Genetic Conditions versus Idiopathic ASD from SFARI Registries

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Background: Recent large-scale initiatives have led to systematically-collected phenotypic data for several rare genetic conditions implicated in autism spectrum disorder (ASD). The onset of developmentally expected skills (e.g., walking, talking) serve as readily quantifiable aspects of the behavioural phenotype. This study's aims were: (1) describe the distribution of ages of attainment of gross motor and expressive language milestones in several rare genetic conditions, and (2) characterise the likelihood of delays in these conditions compared to idiopathic ASD.

Methods: Participants ages 3 years and older were drawn from two Simons Foundation Autism Research Initiative (SFARI) registries that employed consistent phenotyping protocols. Inclusion criteria were a confirmed genetic diagnosis of one of 16 genetic conditions (Simons Searchlight) or absence of known pathogenic genetic findings in individuals with ASD (SPARK). Parent-reported age of acquisition of three gross motor and two expressive language milestones was described and categorised as on-time or delayed, relative to normative expectations.

Results: Developmental milestone profiles of probands with genetic conditions were marked by extensive delays (including non-attainment), with highest severity in single gene conditions and more delays than idiopathic ASD in motor skills. Compared to idiopathic ASD, the median odds of delay among the genetic groups were higher by 8.3 times (IQR 5.8-16.3) for sitting, 12.4 times (IQR 5.3-19.5) for crawling, 26.8 times (IQR 7.7-41.1) for walking, 2.7 times (IQR 1.7-5.5) for single words, and 5.7 times (IQR 2.7-18.3) for combined words.

Conclusion: Delays in developmental milestones, particularly in gross motor skills, are frequent and may be among the earliest indicators of differentially affected developmental processes in specific genetically defined conditions associated with ASD, as compared to those with clinical diagnoses of idiopathic ASD. The possibility of different developmental pathways leading to ASD-associated phenotypes should be considered when deciding how to employ specific genetic conditions as models for ASD.

Keywords: Idiopathic Autism Spectrum Disorder, developmental phenotype, genetic conditions, gross motor milestones, expressive language milestones, developmental delays

POSTER 27: Clinical and Behavioural Features of SYNGAP1-Related Intellectual Disability: A Parent and Caregiver Description

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Background: *SYNGAP1*-related Intellectual Disability (ID) is a neurodevelopmental disorder that is caused by mutation of the *SYNGAP1* gene and is said to account for between 0.5-1% of all sporadic cases of ID. Due to the relatively recent reporting of this condition, we aim to highlight the clinical and behavioral features of this prevalent neurodevelopmental disorder.
Methods: We conducted semi-structured interviews with 27 parents and care givers who had a child with *SYNGAP1*-related ID. The interview covered basic information (e.g. age, gender, genetic variation), family history, perinatal history, past medical history, developmental history, epilepsy, behavioral history, and a general description of their child's behavior.
Results: Using a mixed methods approach, the responses from the parents indicated that those with *SYNGAP1*-related ID showed high rates of autism spectrum disorder (52%), deficits in fine and gross motor skills, delays in language development, and a high prevalence of epilepsy (70%). A qualitative analysis highlighted that their sensory profile involved audio, visual, gustatory, and proprioceptive themes whilst their general behavior concerned the themes of daily living skills, distress-related behaviours, emotional regulation, difficulties with change, lack of danger awareness and sensory differences.
Conclusion: Our findings and behavioral descriptions provide important insights as well as implications for the diagnosis and care of those with *SYNGAP1*-related ID.

Keywords: SYNGAP1-related ID, behavioral phenotype, intellectual disability, autism

SSBP Syndrome Sheets 2021

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). 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). A few cases have been reported of mosaic imprinting defect, which results in partial methylation of the imprinting centre (see Le Fevre *et al.*, 2017 for case reports). The genetic association between Angelman syndrome and Prader-Willi syndrome has evoked interest in genomic imprinting (see Brown & Consedine, 2004; Haig & Wharton, 2003 for an excellent discussion).

Many of the features of the syndrome are thought to result from impaired expression of UBE3A. This gene is found throughout the brain and has a role in proteic scavenging processes. This expression is normally determined epigenetically by a methylation pattern which is specific to the maternally inherited chromosome. Abnormal imprinting in various regions of the brain and the cerebellum are probably responsible for most of the phenotype. Angelman syndrome phenotype has been associated with mutations in the X-linked methyl-CpG-binding protein 2 (MECP2) which has been implicated in Rett syndrome.

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).

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. Early onset of seizures in Angelman

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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). Abnormal EEG is found in most cases of Angelman syndrome (Boyd, Harden, & Patton, 1988) regardless of the presence of seizures (Laan & Vein, 2005).

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).

Cognitive aspects

Angelman syndrome is associated with a severe to profound intellectual disability, with deficits found in all areas of adaptive behaviour and cognition (Gentile *et al.*, 2010; Peters *et al.*, 2004). Comparisons across cognitive skills suggest relative strengths in socialisation (Peters *et al.*, 2004) and deficits in learning and attention (Jiang *et al.*, 2010; Walz & Benson, 2002). Although broad communication difficulties are shown (Clayton-Smith & Laan, 2003), Angelman syndrome is associated with particular deficits in expressive language; the majority of children and adults are non-verbal with limited alternative communication skills (Calculator & Black, 2010; Jolleff & Ryan, 1993; Penner, Johnston, Faircloth, Irish, & Williams, 1993).

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 and ICD and UPD are reported to have the least severe phenotype and 'atypical' phenotype (Fridman, Varela, Valente, Marques-Dias & Koiffmann, 2002; Gentile *et al,* 2010; Lossie *et al.*, 2001; Mertz *et al.*, 2014). UBE3A mutations, 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).

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 August 2017)

Autism Spectrum Disorder

Classification

Autism Spectrum Disorder (ASD) is a pervasive developmental disorder characterized by deficits in reciprocal social interaction and communication, and the presence of restricted and repetitive behaviour patterns (Diagnostic and Statistical Manual [DSM]-5; American Psychiatric Association, 2013). DSM-5 diagnostic criteria require individuals to show (currently or by history) persistent deficits in: (A) Social communication and social interaction across multiple contexts and (B) Restricted, repetitive patterns of behaviour, interests or activities. To meet criteria for domain (A) individuals must show deficits in: (i) emotional reciprocity, (ii) non-verbal communicative behaviours used for social interaction, and (iii) in developing, maintaining and understanding social relationships. To meet criteria for domain (B) they must show difficulties in at least 2 of the following: (i) stereotyped or repetitive motor movements, (ii) insistence on sameness; inflexible adherence to routines or ritualized patterns of verbal or non-verbal behaviour, (iii) highly restricted, fixated interests that are abnormal in intensity or focus, and (iv) hyper- or hypo reactivity to sensory input or unusual interests in sensory stimuli.

Symptoms must cause clinically significant impairment in social, occupational or other important areas of current functioning and are rated by severity ('requiring very substantial support"; "requiring substantial support" and "requiring support"). Symptoms must also have been present in early development although they may not become apparent until social demands exceed the individual's capabilities. Diagnostic ascertainment should also specify if the autism is accompanied by additional intellectual or language impairments; is associated with a known medical, or genetic condition or environmental factor; is associated with another neurodevelopmental, mental or behavioural disorder, or with catatonia.

Sub-categories of disorder that were previously included in DSM-IV (e.g. Asperger Disorder, Autistic Disorder, Pervasive Developmental Disorder NOS) are no longer specified in DSM-5. However, DSM-5 notes that "Individuals with a well-established diagnosis of autistic disorder, Asperger's disorder or Pervasive Developmental Disorder should be given a diagnosis of Autism Spectrum Disorder"

Associated conditions

There is a significant association between ASD and a number of other developmental and genetic disorders including ADHD, Tuberous Sclerosis and Fragile X. There are links, too, with conditions such as maternal rubella, cytomegalovirus and phenylketonuria although the phenotype in these cases tends to be atypical (Rutter, 2013). There is an increased risk of epilepsy in ASD, especially among individuals with comorbid intellectual disability (estimated rates 20 – 30%). ASD is also more common in individuals with epilepsy and among their siblings and children, than in the general population, indicating shared aetiology and overlapping inheritance (El Achkar & Spence, 2015).

Regression in development, usually around the age of 12 to 24 months, has been reported in many studies. Although estimated rates vary, a recent meta-analysis suggests that a significant loss of skills egression occurs in around 32% of young children with ASD. The most common forms of regression affect social and /or language development (Barger *et al.*, 2013).

Genetics

The risk of ASD in siblings of probands is significantly increased and there is a high concordance rate in monozygotic twins. Family studies indicate that the "Broader Autism Phenotype" (i.e. having problems related to social, language and/or cognitive functioning) occurs in up to 20% of first-degree family members. Although ASD is highly heritable 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 (CNV's; i.e. submicroscopic chromosomal deletions or substitutions). 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 ASD appear to be associated with a known genetic mutation (Bourgeron, 2016; Krishnan, *et al.*, 2016).

More recently, research has begun to focus on the impact of gene-environment interactions and a number of potential environmental risks has been identified (Mandy and Lai, 2016). 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 ASD

Prevalence

Data from epidemiological studies are variable, with recent estimates ranging from 1 in 68 (Christensen *et al.*, 2016) to 1 in 145 (Hill *et al.*, 2015). The latter figure is based on studies of all ASDs combined, conducted in different regions and countries by different teams, although the authors acknowledge that this is a conservative estimate. UK data indicate that the combined prevalence of ASD in adults of all ages in England was 11/100 (95% CI 3–19/1000); rates were higher in individuals with moderate to profound intellectual disability

Physical Phenotype

There is no distinct physical phenotype although minor physical anomalies and dysmorphic features are common. Data suggesting enlarged head circumference and atypical patterns of cerebellar developmental (e.g. Courchesne *et al.*, 2011) are inconsistent (Dinstein, *et al.*, 2017). There are, however, increased rates of chronic and acute medical problems across the life span (Jones *et al.*, 2016).

Life expectancy/natural history

Premature mortality, especially among individuals of lower IQ, has been reported in a number of recent studies (cf Hirvikoski, *et al.*, 2016). Increased mortality is associated with a range of disorders of the nervous, circulatory, respiratory and digestive systems. Epilepsy is the most common cause of early death in individuals of low IQ. In high-functioning individuals with ASD there is an increased risk of suicide.

Behavioural and cognitive characteristics

ASD is defined by impairments in reciprocal social communication and the presence of ritualistic and stereotyped behaviours/interests. Onset of language is typically delayed but significant delays in language are less common in children of average or above IQ. Although frequently associated with intellectual impairment, up to 50% of individuals with ASD are of average intellectual ability (Brugha *et al.*, 2016). In children, non-verbal IQ is frequently higher than Verbal IQ but this pattern may be reversed in older, more able individuals.

Outcome

Longitudinal studies indicate that many individuals, especially those who are more able, 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 and Magiati, 2017). Studies focusing on quality of life generally indicate that this is poor (Ayres *et al.*, 2017). Mental health problems, especially related to anxiety and depression, often emerge in late adolescence/ early adulthood. Estimated rates of mental health disorders vary widely but are generally between 40%-60% depending on the samples studied (Moss *et al.*, 2015; Russell *et al.*, 2016).

Websites:

- www.nas.org.uk
- www.researchautism.net
- www.autistica.org.uk

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Patricia Howlin, August 2017,

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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.

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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

Coffin-LowrySyndrome

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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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).

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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

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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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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

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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 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
Updated by T McLachlan & J Moss; April 2021

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

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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

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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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Annapia Verri, September 2014

Updated by Rosalyn Hithersay, Sarah Pape and Andre Strydom 2019

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

not due to nutrition, disproportional low weight-to-height ratio. FAS has the classic facial features, ARND does not have the facial features. Increasingly however with the use of newer technologies such as 3d facial mapping the landmarks that were described as associated in the past are becoming much easier to quantify and measure. Features such as flat midface and micrognathia are increasingly possible to quantify against normal populations and are being seen more commonly, even when classical facial stigmata are absent(25).

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

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

Neuropsychological Deficits

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

Brain structural abnormalities

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

Brain neurotransmitter and neurophysiological abnormalities

Diffuse CNS neurotoxic effects include cell death and/or disruption of cell migration, proliferation, differentiation and maturation (3,5, 8, and 9). Deficits have been discovered in all neurotransmitter systems. Dopaminergic and noradrenergic deficits are likely connected to ADHD presentation of FASD (4,12,15).EEG abnormalities show infant/ child cerebral immaturity, sleep state EEG, as well as temporal lobe dysrhythmia and complex partial seizure disorder in 6 to 19 year olds with FASD (1,12).

Available guidelines for behavioral assessment/ treatment/management strategies

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

Useful websites /associations for more information

- www.nofas.co.uk
- www.fasd.ie
- www.nofas.com
- www.nofasd.org.au

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Raja Mukharjee, Kieran D O'Malley, May 2015
Updated Raja Mukherjee, July 2019

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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

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
Updated Randi Hagerman MD, May 2019

47,XXY (Klinefelter Syndrome)

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 firm 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.

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. Of those diagnosed, less than 10% of cases were diagnosed before puberty (Bojesen & Gravholt, 2007). However, 47,XXY may be prenatally diagnosed through cytogenetic analysis after amniocentesis or chorionic villus sampling. It may also be prenatally detected through noninvasive prenatal testing (NIPT) and then confirmed prenatally or postnatally. After pregnancy, 47,XXY may be diagnosed through a chromosome karyotype also performed by a blood sample or by a chromosomal microarray (CMA) test. A CMA test consists of a blood sample or oral cheek (buccal) swab. Cheek swab is 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

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child postnatally diagnosed (Samango-Sprouse *et al.*, 2015). School aged children frequently show problems with anxiety and mood dysregulation, self-esteem, and socialization. Socialization problems 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 dysfunction (Ross *et al.*, 2014; Samango-Sprouse *et al.*, 2011, 2013, 2015, 2018).

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 impaired 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 mean IQ values that fall within the normal to low normal range.

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. 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. Because of 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. It 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/xxx/
- 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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Updated: The Focus Foundation, USA, 2017

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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.

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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 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.

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Forms of self-injury include eye-poking, head banging, fingers in wheelchair spokes, and extension of arms in doorways. Emotional self injury, or outwardly directed aggressive behaviors, include hitting, kicking, head-butting, biting others, spitting, swearing, ethnic slurs, inappropriate remarks to the opposite sex, frequently changing opinions, and/or lying.

When oral self- injury is present, removal of the teeth is essential to prevent facial disfigurement. 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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(Prepared by Gary E. Eddey, August 2014

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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Fact sheet updated by David Mowat, 2021.
Fact sheet updated by Liz Evans, Meredith Wilson and David Mowat, March 2014.

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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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Updated by Stephan Huijbregts 2019
Stephan Huijbregts 2015

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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-

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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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Updated by Sarita Soni, April 2019

Updated by Sarita Soni, May 2015

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.

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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)

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

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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Updated, Leopold M.G. Curfs, 2021
Gillian Townend & Friederike Ehrhart : 2016

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

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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 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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Updated by Dr. Maarten Otter, Psychiatrist, 2020
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

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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

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22q11.2 Deletion Syndrome (Velo-Cardio Facial Syndrome)

First descriptions and alternative names

As is so often the case, chromosome 22q11.2 deletion syndrome (22q11.2DS) was first described independently by several perceptive clinicians back in the 1950s to 1970s. As these clinicians were experts within different specialties and therefore not focussing on the same medical problems, several constellations of features were described as separate conditions. The first person to describe children who most likely had 22q11.2DS was the otolaryngologist (i.e. ear nose and throat specialist) Eva 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 congenital malformation first described by Wolf *et al.* and Hirschhorn *et al.* in 1965, independently of one another. It is produced by the loss of genomic material at the telomere of the short arm of chromosome 4.

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 subtelomeric regions are likely to be involved in deleterious chromosomal rearrangements. Deletion size in WHS varies, is most often telomeric, but may be interstitial. The size of the deletion has been associated with the severity in the phenotype. Of the 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. WHSC1 and SLBP are both involved in histone metabolism, and therefore might affect the expression of other genes. Hence, it is possible 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 target genes.

Prevalence and Mortality

The genotype is relatively rare – estimates of its prevalence range from 1:20,000 – 50,000 – and results from a deletion at or near the 4p16.3 locus. 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 Features

Clinical characteristics of the phenotype include growth retardation, hypotonia, unusual idiosynchratic distinctive craniofacial features - "Greek warrior helmet" – that are the combined result of microcephaly, broad forehead, prominent glabella, hypertelorism, high arched eyebrows, short philtrum and micrognathia. In addition, most individuals with WHS are prone to seizures, have mild to profound intellectual disability [ID], and limited, if any, expressive speech and language.

Behavioral and Neuropsychological characteristics

Attention deficits are observed in all subjects and adaptive behavior levels were extremely limited. 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. On the other hand, they often have significant social problems, as assessed by the Conners Parent Rating Scale and Child Behavior Checklist. Limited attention span among children with WHS likely has a negative impact on their short-term memory skills. To that extent, these difficulties are not unique to the WHS phenotype. The proportion of children with WHS with autism or autistic-like features is significantly lower than the rates of autism found in the other subtelomeric disorders such as 2q37, 8p23 and 11q22 – 25 (Jacobsen syndrome).

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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,XXY may be prenatally diagnosed through cytogenetic analysis after amniocentesis or chorionic villus sampling. It may also be prenatally detected through noninvasive prenatal testing (NIPT) which then must be confirmed. Postnatally, 47,XYY may be diagnosed through a chromosome karyotype analysis performed by a blood sample or by a chromosomal microarray (CMA) test. A 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, 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. 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 a high rate of diagnosis of Attention Deficit Disorder (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 studies have been confounded by many factors. Further investigation is needed 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

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function, is increased in boys with XYY vs. 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. Reading may be particularly affected. Difficulties with attention and impulse control are frequently reported.

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).

Neuroimaging

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).

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 loves parallel a high prevalence of language-based learning difficulties, 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.

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. 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. Behavioral therapy or medication for boys may be prescribed for 47,XYY boys with ADHD and/or behavioral problems. Hormonal therapy may be also recommended to supplement development and growth.

Useful websites/associations for more information

- The Association for X and Y Chromosome Variations (AXYS)
  https://genetic.org/variations/about-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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Updated: Focus Foundation, USA, 2017

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Acknowledgements

We are extremely grateful to the wide range of people who contributed to this conference. A few specific acknowledgements are warranted:

- **Honey Heussler**, **Pat Howlin** and **Flora Tassone**, the Organising team of the conference.
- **Liz Walmsley**, the SSBP Administrator
- **Rebecca Windram**, the SSBP Conference Administrator
- **Deborah White**, our graphic designer from Department of Shapes & Colours
- **Damien McNamara**, our web designer from *Flowdigital*
- **Julian Windram**, for help with Gather
- **Members of the Scientific Committee**, for review of abstracts and posters
- **All keynote speakers**, for their time and expertise
- **The JIDR team**
- **SSBP Trustees** and **Executive Committee**

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Developmental disorders and behavioural phenotypes across the lifespan

The Society for the Study of Behavioural Phenotypes will be holding their 24th Research Symposium in Oslo, Norway, on the 9th and 10th September 2022, the Education Day will be on 8th September. The theme will be: Developmental disorders and behavioral phenotypes across the lifespan.

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