26th SSBP International Research Symposium

Programme Book

5th - 7th September, Bali, Indonesia

Save the date!

27th SSBP International Research Symposium will be held in Amsterdam, the Netherlands 4th–6th September 2025

Abstract submission opens: March 2025
Registration opens: April 2025
Deadline for online abstract submission: 16th May 2025
Deadline for discounted earlybird registration: 25th July 2025

Educational Day: 4th September 2025
Research Symposium: 5th–6th 2025

Join us in Amsterdam, the Netherlands for our 27th research symposium. The theme will be: *Towards Personalised Care for Rare Genetic Disorders*

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

The Society for the Study
of Behavioural Phenotypes

5th – 7th September 2024

The 26th SSBP International Research Symposium

Bali, Indonesia

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Welcome from the Conference Organisers

We are delighted to welcome you to the 26th Society for the Study of Behavioural Phenotypes International Research Symposium and Educational Day, held in Bali, Indonesia.

Bali is known as 'The Island of Gods', and 'The Last Paradise on Earth', due to its beautiful landscapes and rich cultural history. With stunning beaches along the length of the coastline, and numerous historic carved temples, there is much to see and do during your visit. You will also experience the famed Balinese hospitality throughout the island.

The theme of the conference this year is Early Identification and Treatment of Genetic and Neurodevelopmental Disorders. We look forward to an exciting program of talks that highlight the importance of early identification, and spotlight a range of diagnostic approaches applicable to healthcare settings around the world. As well as a fantastic range of global speakers, we are delighted to have a number of Indonesian speakers presenting work on local studies. The society welcomes opportunities to forge new partnerships between those clinicians and researchers across the world with a focus on Behavioural Phenotypes. Keynote speakers from India, Thailand, Malaysia, Australia and the USA headline what promises to be a great conference. I am really excited about the program and the opportunities this 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 26th Research symposium.

We hope you enjoy your time in Bali.

H. Heussler, T. I. Winarni, A. Utari, N.R.B. Sihombing, N. Maharani, T.A. Sumekar
SSBP Chair & Conference Coordinators

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Conference Organisers

Professor Tri Indah Winarni

She is a general physician and academic staff at Center for Biomedical Research (CEBIOR), Faculty of Medicine Universitas Diponegoro. Her research is mainly on genetics in intellectual disability especially Fragile X syndrome and associated conditions and obtained her PhD program at Universitas Diponegoro. She has been trained in cytogenetics at Human Genetics Department of Radboudumc, Nijmegen, The Netherlands and Fragile X syndrome and associated conditions at The MIND Institute, UC Davis, USA. Community genetics is now become her research interest, especially exploring the impact of genetics disorders on the community.

Dr. Agustini Utari

Agustini Utari, MD, MSc, PhD is a consultant paediatric endocrinologist, the Head of the Pediatric Endocrinology Division and the Coordinator of the Master's Program in Genetic Counseling at Diponegoro University, Semarang, Indonesia. She earned her medical degree and specialization in Pediatrics from Diponegoro University and completed her Paediatric Endocrinology Consultant at Universitas Indonesia, Jakarta. She pursued a fellowship at the MIND Institute, University of California Davis, USA (2008-2009), focusing on Fragile X and Autism Spectrum Disorders. She obtained her Ph.D. from Diponegoro University in collaboration with Radboudumc, Nijmegen, the Netherlands, specializing in Congenital Adrenal Hyperplasia (CAH). Her current research focuses on CAH, Newborn screening, Down Syndrome, Turner syndrome, and multiple congenital anomalies.

She was a co-chair of APPES - CLAN (Caring and Living as Neighbours) Equity Working group during 2017-2019 and a Technical Advisory Group (TAG) Non Communicable Disease of APPA (2016-2018). Currently, she serves as Vice President of Global Pediatric Endocrinology and Diabetes (GPED) and is a member of the Strategic Advisory Group (SAG) on Non-Communicable Diseases and Mental Health for the International Pediatric Association (IPA). She is also a board member of the Pediatric Endocrinology Working Group of the Indonesian Pediatric Society, a member of the National Expert Commission of the Indonesian Newborn Screening Program, and serves on the Public Education Committee of the Indonesian Society of Human Genetics (InaSHG).

Dr Nydia Rena Benita Sihombing

Nydia is a medical doctor, human genetics researcher at Center for Biomedical Research (CEBIOR), and academic staff at Department of Anatomy, Faculty of Medicine, Universitas Diponegoro, Indonesia. She obtained her degree on Medical Doctor in 2015, Master of Biomedicine majoring in Genetic Counseling in 2017, and Doctor of Medicine in 2020, all of which from Universitas Diponegoro. Her research topics are mainly on the genetics of intellectual disability (ID) and multiple congenital anomalies (MCA), specifically fragile X syndrome and other syndromic ID.

Dr Nani Maharani

She graduated as a medical doctor from Faculty of Medicine, Universitas Diponegoro in 2006. Her Master's degree was obtained from the same university, under Master Program on Biomedical Science, majoring Genetic Counseling. Her Master research was on Marfan Syndrome and related disorders, performed in the Department of Clinical Genetics, Vrije Universiteit, Amsterdam, The Netherlands. She did her Ph.D study in the Department of Genetic Medicine and Regenerative Therapeutics in Tottori University, Japan, with research on cardiac ion channels in arrythmia. Her current research interests include cardiovascular abnormalities in genetic syndromes such as Noonan Syndrome, DiGeorge Syndrome, etc, as well as personalized medicine in cardiovascular and genetic diseases.

Dr Tanjung A. Sumekar

She is academic staff at Faculty of Medicine Universitas Diponegoro and psychiatrist at Diponegoro National Hospital. She graduated as a medical doctor from Faculty of Medicine, Universitas Diponegoro. Her Master's degree was obtained from the same university, under Master Program on Biomedical Science, majoring Genetic Counseling. Her Master research was on Fragile-X Syndrome and other neurodevelopmental disorders, performed in UC Davis MIND Institute, USA. She did her specialist program at the Department of Psychiatry, Universitas Diponegoro. Her current research is community and genetic psychiatry.

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Associate Professor Honey Heussler

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

Professor Randi Hagerman

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

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Scientific Committee

The SSBP

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

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

Meetings of the SSBP

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

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

Forthcoming Meetings of the SSBP

2025	Amsterdam, the Netherlands	27th International

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The SSBP Executive Committee

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 Jane* ***Waite*** (UK) (j.waite@aston.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) (rjhagerman@ucdavis.edu)
	Dr Laura ***Roche*** (Australia) (Laura.roche@newcastle.edu.au)
	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) (rjhagerman@ucdavis.edu)

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

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

Tom Oppé and the Tom Oppé Distinguished Lecture

Tom Oppé

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

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

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

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

Tom Oppé Lecturers

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

2024 Tom Oppé Distinguished Lecturer: Dr Gauri Divan

Gauri Divan, MBBS, MRCPCH, is the Director of the Child Development Group at the non-governmental organisation Sangath, and her work as a developmental paediatrician focuses on child development, developmental disabilities and adolescent health. The aim of her work is to consider the design and evaluations of scalable interventions in resource poor settings.

Her work in the area of developmental disabilities has considered how best to support families of young children with autism in their care journey. The 'Parent-mediated Autism Social Communication Intervention for non-Specialists Plus (PASS Plus),' uses video feedback to support parents to understand their child's social communication needs which then helps them create a more supportive communication environment for their autistic child. Divan as a co-lead investigator has been awarded, in partnership with the University of Manchester a prestigious National Institute for Health and Care Research (NIHR) award, for the project NAMASTE which aims to design a community based detection care pathway for young children with autism across 4 sites in India, Sri Lanka and Nepal over the next 5 years (2022-2027).

She is on the technical resource group to design a National strategy for Autism care, Government of India and was a member of the Lancet Commission on the Future of Care and Research in Autism, 2019-2021. She is a Fellow of the International Society for Autism Research.

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.

2024 Pat Howlin Lecturer:
The Patricia Howlin Lecture Prize has not been awarded in 2024, as no eligible abstracts were submitted. The SSBP would like to encourage any students or early stage researchers working on intervention-based research to consider submitting an abstract for consideration at the SSBP 2025 conference.

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 £200 (or equivalent) and an award certificate - both of which will be presented to the winner during the SSBP Research symposium.

Patricia Howlin Lecturers

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

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Petrus de Vries and the Leclezio-de Vries Lecture

Petrus J de Vries

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

The Leclezio-de Vries Lecture:

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

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

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

The award is judged by the Organising Committee of each Research Symposium who make a recommendation to the SSBP Executive Committee at least 1 month prior to the SSBP Research Symposium. Once approved by the SSBP Executive, the successful candidate will be invited to present the Lecture.
The award winner receives free registration for the current SSBP Research Symposium along with a prize of £200 (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

2024	Talia Thompson
2023	Jeanne Wolstencroft
2022	The TAND Consortium
2019	Ms Siobhan Blackwell

2024 Leclezio-de Vries Lecturer: Dr Talia Thompson

Talia Thompson is an Assistant Professor of Pediatrics at the University of Colorado School of Medicine and a licensed psychologist with Children's Hospital Colorado. She is also a clinical and translational research scientist with a focus on psychosocial development and quality of life in rare pediatric genetic conditions. She uses community-engaged, qualitative, and strengths-based methods, to produce meaningful research grounded in the priorities of the community. Dr. Thompson also serves as a qualitative methodologist with the Child Health Biostatistics Core and the Adult and Child Center for Outcomes Research and Delivery Science (ACCORDS), supporting investigators across the CU Anschutz Medical Campus with mixed methods study designs.

Other SSBP Prizes and Awards

The James Harris Scholarship

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

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

The James Harris scholarship was created and first awarded in 2023 to support a member of the SSBP from a LMIC country to attend the SSBP meetings. Each year, the scholarship will be awarded to the author of the highest scoring abstract received from an SSBP member from an LMIC country, as scored by the scientific committee. The James Harris Scholarship will cover registration, and £200 (or equivalent) towards travel and accommodation costs.

2024 James Harris Scholarship Winner: Dr Nola Chambers

Nola Chambers is a South African speech and language therapist and senior research officer at the Centre for Autism Research in Africa (CARA) at the University of Cape Town. Her main areas of research include the early signs of autism in young South African children and supporting and coaching parents in how to promote social communication and learning in their young children with autism, particularly in low resource settings. She is also a member of the TAND consortium, an international group of researchers, clinicians and family representatives investigating the neuropsychiatric difficulties associated with tuberous sclerosis complex.

The Martin Bax Poster Prize

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

Sponsors

The SSBP is extremely grateful to the following organisations for their sponsorship of SSBP 2024 in Bali.

Venues

Educational Day (5th September)

Research Symposium (6th–7th September)

The Educational Day and The Research Symposium will be held at:
Grand Hyatt Bali, Karangasem Ballroom
Kawasan Wisata Nusa Dua BTDC,
Bali 80363, Indonesia
+62 361 771234

Welcome Reception (5th September)

The Conference Reception will be held at:
Grand Hyatt Bali - Negara Room

Conference Visit and Dinner (6th September)

The Conference Dinner will be held as part of a conference visit to Uluwatu Temple. We will travel together by bus to Uluwatu temple, where we will watch a traditional Kekac Dance ceremony, before having dinner together on Jimbaran Beach. We will return to the Grand Hyatt by bus at the end of the dinner.

Keynote Speaker Profiles:

(in order of presentation)

Dr Gemma Davy

Dr. Gemma Davy is a Senior Project Officer at the Murdoch Children's Research Institute, based at the Royal Children's Hospital, and an Adjunct Research Fellow at the Olga Tennison Autism Research Centre at La Trobe University, both located in Melbourne, Australia. Her research is dedicated to improving the quality of life for Autistic children and their families, with a focus on understanding their experiences during the early years following diagnosis. Gemma also works to enhance early childhood services by improving service delivery to promote better developmental, health, and well-being outcomes for all children. This work involves co-leading the implementation of the Restacking the Odds Initiative, a data utilization and continuous improvement program, across remote, regional, and metropolitan communities throughout Australia.

Dr. Agustini Utari

Agustini Utari, MD, MSc, PhD is a consultant paediatric endocrinologist, the Head of the Pediatric Endocrinology Division and the Coordinator of the Master's Program in Genetic Counseling at Diponegoro University, Semarang, Indonesia. She earned her medical degree and specialization in Pediatrics from Diponegoro University and completed her Paediatric Endocrinology Consultant at Universitas Indonesia, Jakarta. She pursued a fellowship at the MIND Institute, University of California Davis, USA (2008-2009), focusing on Fragile X and Autism Spectrum Disorders. She obtained her Ph.D. from Diponegoro University in collaboration with Radboudumc, Nijmegen, the Netherlands, specializing in Congenital Adrenal Hyperplasia (CAH). Her current research focuses on CAH, Newborn screening, Down Syndrome, Turner syndrome, and multiple congenital anomalies.

She was a co-chair of APPES - CLAN (Caring and Living as Neighbours) Equity Working group during 2017-2019 and a Technical Advisory Group (TAG) Non Communicable Disease of APPA (2016-2018). Currently, she serves as Vice President of Global Pediatric Endocrinology and Diabetes (GPED) and is a member of the Strategic Advisory Group (SAG) on Non-Communicable Diseases and Mental Health for the International Pediatric Association (IPA). She is also a board member of the Pediatric Endocrinology Working Group of the Indonesian Pediatric Society, a member of the National Expert Commission of the Indonesian Newborn Screening Program, and serves on the Public Education Committee of the Indonesian Society of Human Genetics (InaSHG).

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Professor Ahmad Suryawan

Prof. Ahmad Suryawan, MD, PhD, is a pediatrician consultant in the field of Growth and Development of Infant and Children. Recently he is the Chairman of Growth and Development – Social Pediatric Working Group, Indonesian Pediatric Society, and he currently serves as Deputy Director of Medical and Nursing Services at Soetomo General Education Hospital, Surabaya.

He graduated as a pediatrician and PhD from Airlangga University, Surabaya, Indonesia. He engaged and studied in the field of early detection of developmental disorders in early age by assessment of General Movements (GMs) method (Basic and Advance Level) and Infant Motor Profile Since 2006 at Beatrix Children Hospital, University Medical Centre Groningen (UMCG), Groningen - The Netherlands. He is certified on Research Methodology & Demography from Mahidol University, Thailand. He is also certified in Newborn Behavior Observation assessment from Brazelton Institute – Harvard Medical School – Boston, USA. Recently, he has taught a child developmental assessment extensively in Indonesia.

His lines of research are: early detection of developmental disorders, brain development in early age, long term growth and developmental outcomes of high-risk infants and the impact of early intervention on typical and atypical development. He ever awarded as "The Winner of Young Researcher Award" in 11th ASEAN Pediatric Federation Conference in 2002. He awarded as a Doctor of the Year Soetomo General Academic Hospital in 2019. Currently he is active in the Council of the International Society for Developmental Origins of Health and Disease (DOHaD) and he has published more than 85 publications in national and international journals as well as several book chapters.

Professor Thong Meow-Keong

Professor Dr THONG Meow-Keong is a Consultant Clinical Geneticist at the University of Malaya Medical Centre. He was a Fulbright Scholar and a board-certified clinical geneticist and established the first Genetics Clinic in Malaysia in 1995. He is the current President of the College of Paediatrics, Academy of Medicine of Malaysia, Vice-President of the Medical Genetics Society of Malaysia, Chair of the Ethics Committee on Medical Genetics of the Malaysian Medical Council and a medical advisor to the Malaysian Rare Disorders Society. He was the previous Chair, Department of Paediatrics, University of Malaya and past President, Asia-Pacific Society of Human Genetics in 2012-2015. He was the recipient of the 2022 American Society of Human Genetics Advocacy Award. He is the current Dean, Faculty of Medicine and Health Sciences, Universiti Tunku Abdul Rahman, Malaysia.

His clinical practice and research are focused on rare diseases, neurogenetic conditions, genomic medicine and genetic counselling. He has published extensively in peer-reviewed journal publications, 5 books, 18 book chapters including the Oxford Monograph in Medical Genetics and an IDEAS White Paper policy document entitled "Rare Diseases in Malaysia". He is a steering committee member of the Global Genomic Medicine Consortium and invited by the World Health Organization and the Ministry of Health Malaysia to advise on issues related to medical genetics. He was elected a Fellow of the Academy of Sciences Malaysia, Fellow of the Academy of Medicine of Malaysia and Honorary Fellow of the Academy of Medicine, Singapore.

Professor Stewart Einfeld

Stewart Einfeld is a Child and Adolescent Psychiatrist. His clinical and research interests have been with children and families affected by developmental disabilities, especially where accompanied by behavioural and emotional problems. This has included research in clinical assessment, intervention monitoring, epidemiology, health promotion, and behaviour phenotypes of genetic syndromes. He has been a co-leader of programs designed to support families affected by developmental disabilities in remote communities and low and middle income countries.

Professor Randi Hagerman

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

Hagerman has written over 500 peer-reviewed articles and numerous book chapters on neurodevelopmental disorders, as well as editing several books on fragile X disorders including a 2020 book edited by Hagerman and Hagerman titled Fragile X Syndrome and Premutation Disorders published by MacKeith press and she coedited the second edition of the Textbook of Autism Spectrum Disorders published by the American Psychiatric Publishing in 2023. Her research includes targeted treatment trials for Fragile X syndrome, autism, FXTAS and other premutation disorders.

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Professor Weerasak Chonchaiya

Professor Weerasak Chonchaiya, M.D., holds multiple roles at Chulalongkorn University in Bangkok, Thailand, including Head of the Center of Excellence for Maximizing Children's Developmental Potential and Deputy Head of Academic Affairs in the Department of Pediatrics. He also leads the Thai Sub-Board of Developmental and Behavioral Pediatrics Fellowship Training Program at the Royal College of Pediatricians of Thailand.

Dr. Chonchaiya earned his M.D. with First-Class Honors from Chulalongkorn University in 1999. He completed his pediatric residency and fellowship in Developmental & Behavioral Pediatrics at Chulalongkorn University in 2007. He then underwent postdoctoral training at the M.I.N.D. Institute, University of California, Davis, and was a visiting scholar at the University of Michigan.

With more than 35 publications and an h-index of 17, Dr. Chonchaiya is a respected reviewer for journals such as Pediatrics, the Journal of Autism and Developmental Disorders, and the Journal of Psychiatric Research. His research focuses on the impact of early childhood adversities, such as inappropriate exposure to electronic media and suboptimal parenting, on child development, behaviors, and executive functions, as well as genomics and proteomics in autism spectrum disorder. His work on the influence of inappropriate electronic media on early childhood development and sleep has influenced the recommendations of the American Academy of Pediatrics. Dr. Chonchaiya actively shares his findings with various stakeholders to raise awareness of the effects of inappropriate exposure to electronic media on children.

Professor Elizabeth Berry-Kravis

Elizabeth Berry-Kravis MD, PhD is a Professor of Pediatrics and Neurological Sciences and Director of the RUSH Pediatric Neurosciences F.A.S.T. Center for Translational Research at Rush University Medical Center in Chicago. She established the Fragile X Clinic and Research Program at Rush University Medical Center in 1992 and has provided care to over 800 patients with fragile X syndrome (FXS). She conducts research on FXS, including genotype-phenotype, molecular, biomarker, outcome measure, and natural history studies, and clinical trials. She has expanded this clinical and translational work to other neurogenetic diseases in the past 10 years, including work on PMS, NPC, Angelman syndrome, Rett syndrome, Batten's disease, PKAN, and creatine transport deficiency. She has led the effort to develop new targeted treatments for FXS and other genetic neurological diseases, including antisense oligonucleotides and gene therapy, and has implemented novel trial designs, including N-of-1 trials.

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Educational Day Programme

Thursday 5th September 2024 – Grand Hyatt Bali - Karangasem Ballroom

08:15	**Arrival and Registration**
08:55 – 09:00	Welcome from the Conference Organisers
	Session 1. Chair: Honey Heussler
09:00 – 09:45	**KEYNOTE: 1. Gemma Davy** - Early identification of autism from infancy to preschool using professional observations and parental report: Developmental surveillance using the SACS and ASDetect tools
09:45 – 10:30	**Free Communications** - 3 x 15 minutes
	2. Aishworiya Ramkumar - Validity and Feasibility of Using the MCHAT-R/F for Autism Screening Among Well Children Within the Existing Primary Care System in Singapore
	3. Charlotte Willfors - Symptoms of Autism in Williams Syndrome: A Transdiagnostic Approach
	4. Nola Chambers - Validation of the Self-Report, Quantified TSC-Associated Neuropsychiatric Disorders Checklist (TAND-SQ)
10:30 – 11:00	**MORNING REFRESHMENTS**
	Session 2. Chair: Tri Indah Winarni
11:00 – 11:30	**KEYNOTE: 5. Agustini Utari** - Down Syndrome in Indonesia: Diagnosis, Early Intervention and Management
11:30 – 12:15	**Free Communications** - 3 x 15 minutes
	6. Ni Wayan Suardani - Balinese Down Syndrome's Stigma
	7. Nani Maharani - Noonan Syndrome: Demographic, Phenotype Characteristics and Diagnosis Odyssey
	8. Epifani Angelina Chandra - Unveiling Turner Syndrome: Clinical Presentation and Late Identification Challenges in Indonesia
12:15 – 13:30	**LUNCH**
	Session 3. Chair: R. Hagerman
13.30 – 14:45	**Free Communications** - 5 x 15 minutes
	9. Poonnada Jiraanont - Population-Based FMR1 Carrier Screening Among Reproductive Women
	10. Tanjung Ayu Sumekar - Modifiable Risk Factors Associated with Autism Spectrum Disorders in Indonesia
	11. David Hessl - Using an App-Based Ecological Momentary Assessment of Executive Function Related Behaviours in IDDs: Preliminary Feasibility, Reliability, Validity, and Factor Structure
	12. Honey Heussler - The Global Angelman Syndrome Registry: An Overview
	13. Van Ma - Neurodevelopmental Spectrum of a Cohort of Individuals with KBG Syndrome
14:45 – 15:15	**AFTERNOON REFRESHMENTS**

	Session 4. Chair: H. Heussler
15:15 – 15:45	**KEYNOTE:** 14. Ahmad Suryawan - General Movements (GMs) methods as a predictive tool of neurodevelopment disorders in early age
15:45 – 16:30	**Free Communications** - 3 x 15 minutes
	15. Lindsay Mizen - Sleep in SYNGAP1-Related Intellectual Disability
	16. Nydia Rena Benita Sihombing - Cri-du-chat (5p) Syndrome Combined with 3q28q29 Duplication: A Case Report
	17. Georgie Agar - Differences in Overnight Caregiving Patterns of Mothers and Fathers: Objective Assessment in Two Rare Genetic Syndrome
16:30 – 17:00	Discussion – Panel session
17:00	Close of Educational Day
17:00 – 19:00	**CONFERENCE WELCOME RECEPTION** – Drinks Reception at Grand Hyatt Bali, Negara Room

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Research Symposium Programme

Friday 6th September 2024 – Grand Hyatt Bali - Karangasem Ballroom

08:30 – 08:55	**Registration for New Arrivals and Poster Set-up**
08:55 – 09:00	Welcome to Research Symposium
	Session 5. Chair: H. Heussler
09:00 – 09:45	**KEYNOTE: 18. Gauri Divan - Tom Oppé Prize Lecture** - Adapting and innovating: a model of autism care for low resource settings
09:45 – 10:30	**Free Communications** - 3 x 15 minutes
	19. Gail Alvares - Targeting Intolerance of Uncertainty in Young Children Diagnosed with Autism: A Randomised Controlled Trial of a Parent-Mediated Group Intervention
	20. Jessica Martin - Anxiety and Challenging Behaviour in Rare Neurodevelopmental Disorders (NDDs): A Focus on DDX3X-related NDD and CASK-related NDD
	21. Irene Astrid Larasati - Correlation Between Uncertainty and Anxiety in Parents of Children with Down Syndrome in a Developing Country: A Cross-Sectional Study in Indonesia
10:30 – 11:00	**MORNING REFRESHMENTS**
	Session 6. Chair: N. Tartaglia
11:00 – 11:20	**22. Talia Thompson – Leclezio Devries Prize** - Recognizing Anxiety in Turner Syndrome Early: Community Engaged Development of a Patient-Centered Outcome Measure
11:20 – 11:50	**Free Communications** - 2 x 15 minutes
	23. Effie Pearson - A Caregiver-Reported Profile of Separation Distress and Attachment-Related Behaviours in Angelman Syndrome
	24. Jessica Hall - Psychopathology, Cognition and Developmental Coordination Disorder Associated with 15q11.2 Deletion
11:50 – 12:15	Discussion
12:15 – 13:30	**LUNCH & POSTER VIEWING**

	Session 7. Chair: S. Shankar
11:00 – 11:20	**KEYNOTE:** 25. Meow-Keong Thong - The Role Of Genomic Counselling And Public Health Genomics In Low and Middle Income Countries in the Asia-Pacific Region
14:00 - 14:45	**Free Communications** - 3 x 15 minutes
	26. Tri Indah Winarni - APOε and KLOTHO Gene Variants Do Not Affect Diagnosis and Severity of Fragile X-Associated Tremor/Ataxia Syndrome Phenotypes
	27. Flora Tassone - Clinical Phenotype and Altered Metabolomic and Proteomic Profiles in Individuals with 22q11.2 Deletion Syndrome
	28. David Godler - Transcriptomic Signatures in Blood and Brain Related to Intellectual Functioning and Behavioural Features of Prader-Willi Syndrome.
14:45 – 15:00	Discussion
15:00 - 15:30	**AFTERNOON REFRESHMENTS**
	Session 8. Chair: A. Utari
15:30 - 16:00	**KEYNOTE:** 29. Stewart Einfeld - Interventions for Families with People with Developmental Disabilities in Low and Middle Income Countries and Remote Areas
Leave at 16:30	**CONFERENCE EXCURSION AND DINNER** – Visit to Uluwatu Temple, Dinner on beach We will meet at Grand Hyatt Bali to **leave at 16:30** and travel together by bus. We will visit Uluwatu Temple, followed by dinner on Jimbaran Beach, before returning to Grand Hyatt Bali.

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Saturday 7th September 2024 – Grand Hyatt Bali - Karangasem Ballroom

08:30 – 09:00	**Registration (for new Arrivals)**
	Session 9. Chair: F. Tassone
09:00 – 09:30	**KEYNOTE: 30. Randi Hagerman** - Metformin: A Promising New Treatment for Fragile X Syndrome
09:30 – 10:15	**Free Communications** - 3 x 15 minutes
	31. Andrew McKechanie - What Can We Learn About Health and Healthcare From Large-Scale, Routinely-Acquired Data in the United Kingdom: Studies in Fragile X Syndrome
	32. Hazel Biag & Ellery Santos - Exploring Electroretinogram (ERG) Alterations as a Novel Biomarker for Fragile X Syndrome: Comparative Analysis of ERG and FMRP Levels among Full Mutation, Premutation, and Healthy Controls
	33. Dejan Budimirovic - FORWARD 2011-2020 Cohort: Frequencies of Non-drug Services in Individuals With Fragile X Syndrome With and Without Co-occurring Autism Spectrum Disorder
10:15 – 10:35	**MORNING REFRESHMENTS**
	Session 10. Chair: S. Einfeld
10:35 – 11:05	**KEYNOTE: 34. Weerasak Chonchaiya** - Global Insights on Screen Media Exposure and 'Virtual Autism': Exploring the Link
11:05 – 11:20	**Free Communications** - 15 minutes
	35. Elizabeth Elliott - Neurodevelopmental and Facial Phenotype and MRI Findings in a Cohort of Early School-Aged Children with Low-Moderate Prenatal Alcohol Exposure
11:20 – 12:15	POSTER SESSION
12:15 – 13:15	**LUNCH**
13:15 – 14:15	**SSBP AGM and Award Ceremony – A presentation about SSBP 2025**
14:15 – 14:25	**SHORT BREAK**
	Session 11. Chair: R. Hagerman
14:25 – 15:15	**KEYNOTE: 36. Elizabeth Berry-Kravis**
15:15 – 15:45	**Free Communications** - 2 x 15 minutes
	37. Sydni Weissgold - Presence and Severity of Challenging Behaviours in SYNGAP1-Related Intellectual Disability
	38. Lauren Shelley - Exploring the Profile of Executive Function Within SATB2-Associated Syndrome to Inform Models of Behavioural Outcomes
15:45 – 16:10	**AFTERNOON REFRESHMENTS**

	Session 12. Chair: H. Heussler
16:10 – 16:55	**Free Communications** - 3 x 15 minutes
	39. Andy Stanfield - Significance of Attention Deficit Hyperactivity Disorder (ADHD) Traits in SYNGAP1-Related Intellectual Disability
	40. Judith Miller - Clinical Characteristics of Creatine Transporter Deficiency (CTD): Final Results of the Vigilan Observational Study
	41. Nicole Tartaglia - Exploring Predictors of 36-month Language and Motor Outcomes in Children Prenatally Diagnosed with Sex Chromosome Trisomy to Inform Early Intervention Trials
16:55	**Closing Remarks**
17:00	**End of Meeting**

Abstracts for Educational Day 5th September *(in order of presentation)*

1. KEYNOTE: Early Identification of Autism From Infancy to Preschool Using Professional Observations and Parental Report: Developmental Surveillance Using the SACS and ASDetect Tools

Presenting Author: Gemma Davy

Barbaro J.[1], Davy G.[1,2]

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[2] Murdoch Children's Research Institute, Melbourne, Australia

Early identification of autism has been found to improve developmental and educational outcomes for children and improve quality of life for families. It is therefore important to identify Autistic children as early as possible. This presentation will cover 20 years of research into the developmental surveillance of autism from infancy to preschool in the general population. It will outline the development, validation, and implementation of three early autism identification tools - Social Attention and Communication Surveillance-Revised (SACS-R) and SACS-Preschool (SACS-PR), used by health and early education professionals from 11-60 months, and ASDetect, a free mobile application for parents and caregivers of children aged 11-30 months.

All three early identification tools have demonstrated robust psychometric properties. At 11-30-months the SACS-R was found to have 83% positive predictive value (PPV; accuracy) and 99% negative predictive value (NPV). Specificity (99.6%) was high with modest sensitivity (62%). When the SACS-PR 42-month assessment was added, sensitivity increased to 96%. Additionally, at 11-30 months, ASDetect was found to have strong psychometrics with 89% PPV and 93% NPV. Specificity was high (97%) with good sensitivity (76%). Further, ASDetect was found to be highly predictive of an autism diagnosis regardless of whether prior caregiver concerns were present or not.

The SACS and ASDetect tools have been translated, culturally adapted, and implemented across 17 counties and settings, particularly the Asia-Pacific and Europe, including lower-resourced settings such as Nepal, Bangladesh, and China.

Developmental surveillance using the SACS-R+SACS-PR and ASDetect have been found to be the most effective methods for the early identification of autism within health, early education, and home settings. Their greater accuracy compared to other commonly used autism screening tools suggests that these tools should be used universally for the early identification of autism. Additionally, increasing parent education on the early signs of autism through tools like ASDetect will empower parents to advocate for further assessment of their child, further improve earlier identification of autism, and ultimately, facilitating positive outcomes for children and their families.

Keywords: Autism; Early Identification; Early Detection; Screening; Developmental Surveillance

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2. Validity and Feasibility of Using the MCHAT-R/F for Autism Screening Among Well Children Within the Existing Primary Care System in Singapore

Presenting Author: Aishworiya Ramkumar

Aishworiya R.[1,2], Zheng R.M.[3], Chan S.P.[2,4], Law E.[1,2,5], Chong S.C.[1,2]

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Background: Autism screening within healthcare systems has challenges including screening fidelity and adherence to post-screening evaluations. Additionally, population-based cultural differences can affect psychometric properties of screening tools.

This study aimed to establish the sensitivity of the Modified Checklist for Autism in Toddlers, Revised with Follow-Up (MCHAT-R/F) for autism screening among well, low-risk children in multi-ethnic Singapore. The secondary aim was to assess feasibility of use within the existing primary-care system.

Methods: Children attending routine 18-month-old well-child visit were recruited at seven primary-care clinics, with inclusion criteria 1. Child age between 17-23 months and 2. Caregiver competency in English. Exclusion criteria was child with known developmental disorder or receiving specialist developmental care. Caregivers completed the M-CHAT-R/F which was scored immediately by research personnel/nursing staff; follow-up interview was administered if required. The standard M-CHAT-R/F scoring protocol was employed. Screen-positive and a subset of randomly-selected screen-negative children underwent a diagnostic evaluation (DE) which included a developmental behavioral pediatrician evaluation and the Autism Diagnostic Observation Schedule (ADOS-2) to confirm an autism diagnosis. Separately, DE was also offered if the primary-care physician had concerns for autism (regardless of M-CHAT-R/F score). All primary-care nurses and physicians completed a feasibility questionnaire that assessed the M-CHAT-R/F's perceived acceptability, practicality and efficacy.

Results: The study sample comprised 5336 children (mean age 18.6 months, SD 0.9, 51.3% male, 64.2% Chinese, 23.9% Malay, 5.8% Indian). In total, 113 (2.1%) children screened positive, of which 63 (55.8%) completed a DE; 54 were subsequently diagnosed with autism. The M-CHAT-R/F's sensitivity was 88.6%, specificity 71.4%, and positive predictive value 90.7%. Feasibility was high especially for efficacy and acceptability.

Conclusion: Results demonstrate acceptable validity of the MCHAT-R/F for autism screening and feasibility of use within an existing healthcare system. Future steps include examining performance at older ages and understanding implementation considerations for a national screening program.

Keywords: Autism, screening, primary care, MCHAT-R/F, sensitivity, positive predictive value

3. Symptoms of Autism in Williams Syndrome: A Transdiagnostic Approach

Presenting Author: Charlotte Willfors

Willfors C.[1,2], Borg J.[3,4,5], Kleberg J.L.[3,6], Hallman A.[1,6], Lundin K.[7], Björlin H.[3], Bölte S.[7,8,9], Nordgren A.[1,2,10]

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Background: Williams syndrome (WS) is associated with atypical social communication and cognition reminiscent of the behaviours observed in autism. Nonetheless, WS also differs significantly from autism, such as regarding social motivation, which is enhanced in WS and reduced in autism. This study sought to examine the conditions' transdiagnostic similarities and differences for autistic symptoms and social functioning, and their developmental trajectories.

Methods: We compared individuals with WS (n=24) and those diagnosed with idiopathic autism (n=24) and attention deficit hyperactivity disorder (ADHD; n=24), aged 9 to 53 years, on measures of autism, social functioning, IQ and co-occurring psychiatric conditions.

Results: Although only 12.5% in the WS group met the criteria for an autism diagnosis, a majority exhibited distinct difficulties within social communication, social cognition, repetitive behaviours, and atypical sensory reactivity resembling autism. Conversely, elevated social motivation and a high number of social initiatives accompany these characteristics. No group differences in the developmental trajectories of autism symptoms were found.

Conclusion: Our results confirm that autistic behaviours are frequent in individuals with WS and give evidence for specific profiles of autistic symptoms associated with the disorder. Hence, emphasizing the need for clinical management of these behaviours in WS.

Keywords: Williams syndrome, Autism, ADHD, social functioning, ASD, transdiagnostic design

4. Validation of the Self-Report, Quantified TSC-Associated Neuropsychiatric Disorders Checklist (TAND-SQ)

Presenting Author: Nola Chambers

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

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Background: The TAND-SQ Checklist allows individuals with tuberous sclerosis complex (TSC) or their caregivers to report and quantify features of TSC-associated neuropsychiatric disorders (TAND). The 33 items reflect seven natural TAND clusters and psychosocial functioning in individuals with TSC and their caregivers. Each item is rated as having ever been present to generate cluster scores (CS), and the item's severity rating in the last month generates cluster severity scores (CSS) and a total TAND severity score (TTSS). We aimed to determine the internal and external validity of the CS, CSS and TTSS.

Methods: Using a descriptive group design, we examined relationships among scores within the TAND-SQ for internal validation and between the TAND-SQ and independent clinical data for external validation. Two convenience samples with clinical data were recruited from the TSC Alliance Natural History Database (NHD) in the US (n=69), and from the Developmental Synaptopathies Consortium Rare Diseases Clinical Research Network (RDCRN) study based at the Boston and Cincinnati Children's Hospitals (n=23).

Results: We found good internal consistency for the CS (alpha: .67-.89) and CSS (.76-.95). Within the TAND-SQ, we found significant relationships between both CS and CSS and corresponding clinical diagnoses, and between the TTSS and a global self-rating of TAND burden. Significant relationships were observed between the CS, CSS, and TTSS and scores on a range of relevant standardised behavioural measures in the RDCRN cohort. Significant relationships were also observed between all CS and corresponding clinical diagnoses of autism, attention deficit hyperactivity disorder, anxiety disorder, depressive disorder, scholastic difficulties, and neuropsychological difficulties reported in both cohorts.

Conclusion: Findings provide support for the internal and external validity of the CS, CSS and TTSS of the TAND-SQ and support their use for guiding clinical decision-making and care for individuals with TSC.

Keywords: Tuberous sclerosis complex; TSC-associated neuropsychiatric disorders; TAND; TAND-SQ Checklist; internal validity; external validity

5. KEYNOTE: Down Syndrome in Indonesia: Diagnosis, Early Intervention and Management

Presenting Author: Agustini Utari

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Background: Down syndrome (DS) is the most common cause of global developmental delay associated with chromosomal abnormality. Some critical conditions in newborns with DS lead to intensive care hospitalization. Early recognition is essential to tailor appropriate management. In Indonesia, the majority of childbirth assistants are midwives and we found a delay in referral, which may contribute to the worst condition. The study aimed to describe the actual problematic condition of DS management in Indonesia.

Methods: A cross-sectional study was conducted in three referral hospitals in Central Java province, Indonesia. Demographic characteristics, anthropometry, diagnosis, and co-morbidities data were collected.

Results: There were 162 DS children, with the mean age of 1.75±2.04 (81 boys) and 1.87±2.26 (81 girls), included in the study. More than half of patients were delivered by obstetrician and 52.5% of mothers have advanced maternal age. Of the cases, 73.5% were from the middle socio-economic level. The early diagnosis of DS (0-3 days) was only found in 41.4% of patients, and almost 20% were diagnosed at six- months and older. Most patients had hypotonia and showed the prominent physical features of DS. Only 10 % of patients confirmed with karyotype. The most common co-morbidities in patients were congenital heart defect (50,6%) and hypothyroidism (55,5%).

Conclusion: This study illustrates the problematical issues of DS management in Indonesia, including advanced maternal age, delayed diagnosis, co-morbidities related to life-threatening conditions, and lack of genetic facilities. It is crucial to improve the knowledge of assisted delivery professionals towards DS in order to make an early diagnosis to enhance optimal management.

Keywords: Down syndrome, Indonesia, Co-morbidities, Early intervention

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6. Balinese Down Syndrome's Stigma

Presenting Author: Ni Wayan Suardani

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[3] Faculty of Psychology, Diponegoro University, Indonesia

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Background: Down syndrome (DS), the most common chromosomal disorder. Incidence rate 1 per 700 live birth and increases every year. The Indonesian National Basic Health Research 2019 shows significant increase in DS cases aged of 24-59 months from 2010 till 2018. Various phenotypes in those with DS makes them even more different from other typical development children. It is easier for them to experience stigma in their lives. Culture and ethnicity impress the stigma level experienced by those with DS and their families. This research aims to understand the stigma level of the Balinese DS and their families occurs since having a DS child.

Method and sample: A cross sectional analytic study was carried out on 41 clinically DS children diagnosed by the paediatricians of Sanglah hospital, Bali registered since January, 1st 2017 until December 31, 2022, and parent signed the informed consent form. A stigma scale questionnaire for DS with good validity and Cronbach's Alpha of 0.928 was used to assess the stigma level. All data were analysed using Jamovi software.

Results: Total stigma score level tend to be low. Median stigma scores significantly difference in some characteristics and the highest median level was in the social interaction subscale. Consanguinity factor, paternal advanced age and educations, developmental delayed was respectively associated with the social interaction, acceptance and health related stigma subscales. Older and educated fathers tend to experience higher stigma level, it may relate to the Balinese local culture "Purusa Pradana" where a man is the successor of the offspring and considered as a failure when they unable to have it.

Conclusion: The Balinese Down Syndrome's stigma tend to be low. Some characteristics significantly associated with stigma level. Local culture may significantly govern the stigma experienced level. Further studies need to be carried out.

Keywords: Down syndrome, Stigma, Balinese

7. Noonan Syndrome: Demographic, Phenotype Characteristics and Diagnosis Odyssey

Presenting Author: Nani Maharani

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Background: Short stature, developmental delay and mild intellectual disability rarely associated with genetic conditions in Indonesia. Noonan Syndrome (NS) is recognized by some features, namely typical facial features, short stature, and congenital cardiovascular abnormalities. NS diagnostic criteria is used in clinical setting to differentiate with other RASopathies syndromes. Clinical manifestations of NS are caused by mutations in either of these genes: *PTPN11, KRAS, SOS1, RAF1, NRAS, BRAF, SHOC2, RRAS, RIT1, LZTR1, SOS2,* or *MEK*, which involve in the Ras-Mitogen-activated protein kinase (Ras-MAPK) pathway. Clinical manifestations are highly variable. Thorough examinations to identify the abnormalities and stepwise molecular diagnosis are needed, as genome sequencing is still limited in terms of facility and cost.

Methods: Forty-eight clinically suspected NS patients were included from the Paediatric clinics and screened based on Van der Burgt criteria for NS. Peripheral blood samples were isolated from antecubital vein for molecular analysis. Preliminary exome sequencing was done on 10 subjects.

Results: Most of the patients were male (64.6%), aged more than 2 years old (70.8%). Twenty-four patients were confirmed as definitive NS, 6 were suggestive NS, while the rests (18) were not fit into the criteria. Short stature was present in 73% of the subjects, congenital heart defect in 66.7%, and facial characteristics of NS in 50% of patients. The most common facial characteristics include low-set ear, hypertelorism, webbed-neck, and down-slanted palpebral fissures. Congenital heart defects include atrial septal defect, pulmonary stenosis, ventricular septal defect, hypertrophic cardiomyopathy, and mitral valve abnormality. Exome sequencing on 8 subjects revealed that *PTPN11* was the causative gene in most of subjects (62.5%), followed by SOS1.

Conclusion: Application of Van der Burgt criteria is the first step of clinical diagnosis. Targeted sequencing on *PTPN11* might be able to solve the causative cause in more than a half of the patients.

Keywords: Noonan Syndrome, Van der Burgt criteria, diagnosis, PTPN11

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8. Unveiling Turner Syndrome: Clinical Presentation and Late Identification Challenges in Indonesia

Presenting Author: Epifani Angelina Chandra

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Background: Late identification of Turner syndrome (TS) poses a significant concern due to its multiorgan involvement. This study aims to elucidate the clinical manifestation, karyotype, and organ involvement in TS patients in Semarang, Indonesia.

Methods: A cross-sectional study combined quantitative and qualitative methods was conducted in TS patients confirmed by karyotyping, assessing age at first presentation and diagnosis, complaints, clinical manifestation, karyotype, uterus ultrasonography (US), bone age (BA), and organ involvement. The qualitative study explored the causes of late identification.

Results: Thirty TS patients were included. The mean age at first presentation and diagnosis was 9.9+5.8 and 10.1+5.9 years old, respectively. Three main complaints at presentation included short stature (32.5%), primary amenorrhea (20%), and dysmorphic features (17.5%). The anthropometric measurement revealed a mean HAZ of -3.82+1.13 SD. Predominant dysmorphic features were widely spaced nipples (80%), low posterior hairline (70%), and low-set ear (63.3%). Karyotypes included 45,X (63.4%), mosaicism (33.3%), and 46,X,iso(Xq) (3.3%). Uterus US (n=20) mostly revealed non-visualized (75%) or hypoplasia (20%) uterus. Hearing loss and ear infection history (6.7%) were found. Cardiac (6/18; 33.3%) and renal abnormalities (8/20; 40%) were found, with coarctation aorta (CoA) (2/6; 33.3%) and horseshoe kidney (5/8; 62.5%) as the main abnormality. The mean BA reduced by chronological age was -31.67+19.84 months old. Qualitative study (n=9) indicated late identification due to parental unawareness (88.9%), normalization of symptoms by parents (55.6%) and their social environment (44.4%), and medical factors such as the doctor's lack of suspicion of TS (77.8%) and focusing on developmental growth (44.4%) or stunting (22.2%).

Conclusion: Short stature and primary amenorrhea are the most common chief complaints, suggesting late identification in addition to various factors. Widely spaced nipples, low posterior hairline, and low-set ears are predominant clinical characteristics. The ear, heart, and kidney evaluation should be done to increase quality of life.

Keywords: Turner Syndrome, Late Identification, Clinical Presentation, Semarang, Indonesia

9. Population-Based FMR1 Carrier Screening Among Reproductive Women

Presenting Author: Poonnada Jiraanont

*Ain Q.[1], Ye H.H.[1], Yeung D.[1], Panpaprai P.[2], Iamurairat W.[2], Chutimongkonkul W.[2], Trachoo O.[3,4], Tassone F.[1,5], **Jiraanont P.[6]***

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Background: Fragile X Syndrome (FXS) is a devastating disorder, commonly caused an inherited intellectual disability (ID) and autism spectrum disorder (ASD). Female carriers or premutation (PM) containing 55-200 CGG repeats can transmit the affected alleles which may expand to full mutation (FM; >200 repeats) in the next generation. There is no PM carrier screening in Thailand. The authors aimed to investigate prevalence of PM carriers among Thai reproductive women at a tertiary hospital.
Method: 1,200 female out-patients participated in this study using blood spot cards with ages ranging from 20-45 years, mean 30 years (S.D.=6.27).
Results: we found two PM carriers with 32, 62 and 32, 69 CGG repeats with no AGG interruptions, equivalent to 1 in 600 females or 0.17% of the population. Furthermore, three gray zone alleles (ranged within 41–54 CGG repeats) were identified with 29,51; 29,49; and 30,47 repeats equivalent to 1 in 400 females or 0.25% of the population. No FM case was detected.
Conclusion: This study heightens the importance of PM carrier screening in the general-based population to prevent ID for children and alert healthcare professionals to handle future problems that may occur with PM carriers including fragile X–associated tremor/ataxia syndrome (FXTAS), fragile X–associated primary ovarian insufficiency (FXPOI) and fragile X-associated neurodevelopmental disorders (FXAND). Early identification of PM carrier status enhances family planning, fecundity alternatives, and improving reproductive health outcomes leading to a better life.

Keywords: FXPOI, FXPAC, premutation, carrier screening, prevalence

10. Modifiable Risk Factors Associated with Autism Spectrum Disorders in Indonesia

Presenting Author: Tanjung Ayu Sumekar

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Background: Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder affecting children worldwide including in Indonesia. The aetiology of ASD is not yet fully understood, however it reflects the interaction between genetics and environment. Objective: This study aims to investigate modifiable risk factors of ASD.
Methods: A case-control study design was done using online survey. The survey was shared through special schools, institutions or health care facilities which provide services for individuals with special needs including ASD, and social media. A total of 277 respondents were included, it comprised of 146 mothers of child with ASD and 131mothers of typical child.
Results: The mean age of children with ASD was 8.0 ± 5.03 and typical children was 6.4 ± 3.80. This study identified factors that associated with ASD including maternal age (OR = 3.0, 95% CI = 1.1 to 8.5), maternal education (OR=7.9, 95%CI= 1.3 to 50.3), maternal occupation (OR = 2.2, 95% CI = 1.2 to 4.1), monthly income (OR = 6.5, 95% CI = 1.6 to 27.1), housing status (OR= 0.5, 95% CI = 0.3 to 0.9), vitamin and folic acid consumption (OR=, 2.5, 95% CI = 1.3 to 4.9), and child medical conditions (OR=6.8, 95%CI = 3.2 to 14.2).
Conclusion: Advanced maternal age, low maternal education, low monthly income, housing status, vitamin and folic acid consumption, and child medical conditions are the modifiable risk factors associated with an increased risk of developing ASD, thus, it requires public consideration in order to do the prevention and appropriate actions.

Keywords: Autism, modifiable, risk factors, environment, genetics

11. Using an App-Based Ecological Momentary Assessment of Executive Function Related Behaviours in IDDs: Preliminary Feasibility, Reliability, Validity, and Factor Structure

Presenting Author: David Hessl

*Dakopolos A.[1], Glassman D.[1], Poudel A.[1], Bass M.[2], Esbensen A.[3], Fidler D.[4], **Hessl D.[1]***

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[2] Feinburg School of Medicine, Northwestern University, USA

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[4] Colorado State University, USA

Background: Executive function (EF) refers to higher order cognitive processes including attention, inhibitory control, cognitive flexibility, working memory, and planning and organization that are often impacted in people with intellectual and developmental disabilities (IDDs). While retrospective proxy-report questionnaires may be susceptible to biases and recall problems, electronic ecological momentary assessments (eEMAs) may provide more accurate data given reporting in near real-time.

Methods: The iBehavior eEMA app was built using Nativescript, and all data collected through the app is encrypted and securely transmitted to REDCap. Twenty-nine EF items were created, with frequency and intensity ratings for each. Respondents included 57 caregivers of children ages 5-17 years old (m = 12.49) with IDD. Caregivers received standardized one-on-one iBehavior training where they learned how to rate each behaviour, and discussed how their child's behaviours fit into 5 EF domains. After training, caregivers completed daily iBehavior ratings for 14 consecutive days. 48 caregivers completed 2 validation measures (Conners-3 and BRIEF-2) covering the same time period, and 56 caregivers responded to a feedback survey.

Results: Participants generally agreed that the app was easy to use, considered items to be relevant to their children, and found it easy to recall behaviours at the end of the day. Although underpowered, a preliminary factor analysis and graphical cluster analysis both showed evidence of meaningful clustering of items. Week 1 to week 2 reliability ICC's were in the high 0.80's to low 0.90's. iBehavior domains that aligned well with BRIEF-2 domains indicated moderately strong correlations. No significant correlations were found between EF iBehavior items and discriminant validation scales.

Conclusion: Though these results are preliminary, stronger associations amongst like-domains indicates good conceptual EF categories in iBehavior, and reliability looks promising. Additional analyses exploring item-level metrics and associations between iBehavior EF and performance-based EF tests (NIH Toolbox Cognition) will be reported.

Keywords: Executive function, fragile X syndrome, Down syndrome, ecological momentary assessment

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12. The Global Angelman Syndrome Registry: An Overview

Presenting Author: Honey Heussler

Heussler H.[1,2], Tones M.J.[3]

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[2] Child Health Research Centre University of Queensland, Brisbane, Australia
[3] eResearch Office, Queensland University of Technology, Brisbane, Australia

Background: Angelman syndrome (AS) is a rare neurogenetic disorder with a prevalence of 1 in 15,000 individuals, or 500,000 individuals worldwide. Global registries are valuable in capturing common patient related information on rare diseases, as they enable patients or their caregivers to contribute information in a safe and accessible manner. Launched in 2016, the Global Angelman Syndrome Registry (GASR) is available in English, Spanish, Traditional Chinese, Italian, Hindi, Brazilian Portuguese and Polish.
Methods: The GASR collects parent and caregiver (hereafter referred to as caregivers) entered data about individuals with AS. Caregivers self-select into the registry via a registration form. After validating their account by email, caregivers complete an online consent form which is available in print and video format. Successful completion of the consent form unlocks the registry forms, enabling caregivers to provide clinical information about their loved one. To enable the multi-language format, the GASR adopted a novel approach using crowd-sourcing and machine translation tools. These translations were then verified by bilingual members of the Angelman and scientific/ clinical communities.
Results: To date, 2406 individuals with Angelman syndrome from 94 countries are registered in the GASR. Of these, 1345 have a diagnosis reported, including Chromosome deletion (64.5%), Mutation (14.6%), Imprinting Centre Defect/ Uniparental disomy (12..8%), Clinical (3.2%), Mosaic (0.7%), Unknown (4.2%).
Conclusion: Findings indicate that the ratios of deletion and non-deletion diagnoses in AS vary by region, suggesting possible differences in awareness of the syndrome, or access to clinical expertise and diagnostic tests. Further research as more families join the registry would create a better understanding of diagnostic patterns and resources worldwide.

Keywords: Rare disease, Angelman syndrome, Patient driven registry

13. Neurodevelopmental Spectrum of a Cohort of Individuals with KBG Syndrome

Presenting Author: Van Ma

Ma V.[1,2], Angkustsiri K.[1,2], Thompson H.L.[3], Thurman A.[2,4], Durbin-Johnson B.P.[5], Hagerman R.[1,2], Akins R.S.[1,2], Shankar S.[1,2]

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Background: KBG syndrome is a rare genetic condition caused by pathogenic variants in *ANKRD11* or deletions on chromosome 16q involving *ANKRD11*. *ANKRD11* encodes an ankyrin repeat domain-containing protein that plays a crucial role in neural development. Clinical characteristics include: congenital anomalies, craniofacial dysmorphism, behavioural challenges, and developmental delay/intellectual disability. More than 150 cases have been reported, but this may be an underestimation as features may be subtle or overlap with other conditions leading to misdiagnoses. To date, no prospective cohort study has described the neurodevelopmental phenotype.

Methods: Children with KBG syndrome were recruited from internal and local clinics. Inclusion criteria included informed consent, ages 5–17 years, and visual and motor abilities to complete the evaluations. Cognitive abilities were assessed using the Differential Ability Scales-2nd Edition (DAS-II), and behaviours were assessed using the Behavior Assessment System for Children-3rd Edition (BASC-3) and Autism Diagnostic Observation Schedule-2nd Edition (ADOS-2).

Results: Four participants (1 F, 3 M) ages 6–13 years were enrolled. On the DAS-II, a basal was not reached for one participant. Individual cognitive profiles indicated that, for two of three participants, verbal scores were higher compared to spatial ability ($p<0.05$), but there was no discrepancy between verbal and nonverbal scores. Nonverbal scores were also higher compared to spatial ability ($p<0.05$) for two participants. For all three participants, the spatial cluster score was the lowest scoring domain. On the BASC-3, inattention was clinically significant for three participants and borderline at risk for one, and hyperactivity was clinically significant/at risk for three. The ADOS-2 overactivity code was elevated for all participants.

Conclusion: In KBG syndrome, cognitive abilities vary greatly, but inattention and hyperactivity symptoms were seen in all participants. Results should be interpreted with caution due to the small sample size. However, findings are largely consistent with current reports in the literature.

Keywords: KBG syndrome, neurodevelopmental phenotype, rare disease

14. KEYNOTE: General Movements Methods as a Predictive Tool of Neurodevelopment Disorders in Early Age

Presenting Author: Ahmad Suryawan

***Suryawan A.*[1]**

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The assessment of the quality of spontaneous movements in newborns, well known as the General Movements (GMs) quality assessment method, has been introduced by Prechtl since the 1990s. Nowadays many experts argue that spontaneous movements of newborns can be used as a source of information about the integrity of the central nervous system or the brain of children at an early age. Two main structures in the developing brain which neurons and glial cells plays a critical role, cortical subplate and its efferent motor connections in the periventricular white matter, already recognized as the putative neural substrate of normal and abnormal GMs. The clinical application of the GMs method has been widely applied in various countries, because this method is not invasive, easy and inexpensive. However, because the assessment of this method uses the gestalt perception of observer, it requires a trained observer through special training. Currently, many studies have proven that GMs quality assessment is an effective method for early detection of child development disorders because this GMs method has very good predictive value for motoric disorders in terms of cerebral palsy, and various child development disorders, such as ADHD, autism, and other behavioral disorders, including cognitive impairment in children.

Keywords: General movements, spontaneous movements, early detection, developmental disorders, predictive value, cerebral palsy

15. Sleep in SYNGAP1-Related Intellectual Disability

Presenting Author: Lindsay Mizen

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[2] NHS Lothian Intellectual Disability Service, UK

Background: SYNGAP-related Intellectual Disability (SYNGAP1) is a single gene condition associated with Intellectual Disability, autism, epilepsy and sleep disturbance. Sleep EEG in SYNGAP1 rat models has shown significantly shorter Rapid Eye Movement (REM) and seizures in quiet wakefulness. We aimed to conduct the first case-control sleep study in SYNGAP1 and hypothesised that cross-species sleep biomarkers would be identified.
Methods: Polysomnography was performed in participants' homes including EEG, electrooculography, electromyography, oxygen levels, pulse, body position and video. Data analysis was in accordance with The American Academy of Sleep Medicine (AASM) guidance.
Results: 15 children with SYNGAP1 and 15 controls between 4-14 years old were recruited UK wide. Sufficient polysomnography data was collected from 12 in each group. REM sleep duration was significantly shorter in the SYNGAP1 group (Controls: median 173.50 minutes, IQR 78.5, SYNGAP1: median 84.5 minutes, IQR 82.38, Mann Whitney U = 14, p = <0.001). Six participants, all with SYNGAP1, had diagnosed epilepsy. In our data, three of the these had confirmed or suspected seizure activity. One event was in probable wakefulness, one started in N2 and transitioned to wakefulness; the others occurred in N2 and N3.
Conclusion: By finding significantly shorter REM sleep, we identified a cross-species biomarker of sleep architecture in SYNGAP1. REM sleep plays a key role in brain and motor development plus emotional and spatial memory. Hence, identifying treatments for reduced REM is particularly important in people with SYNGAP1 who already face significant cognitive challenges. There was a suggestion of seizures in quiet wakefulness, again mirroring rat data, but few potential events were noted and further studies are needed. A larger sample size is also required to study variables such as age and use of hypnotics. Medication trials aiming to ameliorate the REM deficit are underway in rats, hence clinical trials are a tangible prospect.

Keywords: SYNGAP1, intellectual disability, sleep

16. Cri-du-chat (5p) Syndrome Combined with 3q28q29 Duplication: A Case Report

Presenting Author: Nydia Rena Benita Sihombing

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Background: Chromosomal aberration comprises around 10-15% aetiology of multiple congenital anomalies (MCA). While some chromosomal abnormalities were seen more frequently, such as Cri-du-chat syndrome, many other syndromes were rarely found, for instance, the 3q28q29 duplication syndrome less than 40 cases were reported. We present a case of both chromosomal aberrations, highlighting the rarity of such a condition, and the need for molecular diagnostic workup to provide answers for the family.

Methods: The patient was included in the MCA research in our centre, using a proposed diagnostic approach for individuals with global developmental delay (GDD) and MCA in Indonesia. Physical and dysmorphology examinations were done by an experienced paediatrician. Chromosomal microarray (CMA) was performed in collaboration with the National Centre for Women and Children's Health Harapan Kita, Jakarta, using Human CytoSNP12 (Illumina).

Results: An 18 months-old female patient was consulted for GDD and failure to thrive. She also had frequent respiratory problems, such as recurrent upper respiratory tract infections, and stridor while in the supine position. The mother recalled a cat-like voice when in infancy. On physical examination, her weight was -4.39 SD, height -2.18 SD, and head circumference -5.26 SD. She had a right ear tag, telecanthus, micrognathia, high and narrow palate, and single palmar creases. None of the abnormality was detected on the echocardiography workup. CMA was done upon suspicion of Cri-du-chat syndrome. The analysis revealed a gain of 8.8 Mb of chromosome 3q28q29 and a loss of 17.8 Mb of chromosome 5p15.33p15.1. The deletion of 5p15.33 resulted in Cri-du-chat syndrome, meanwhile, clinical characteristics of 3q28q29 duplication syndrome were highly heterogeneous. Some overlapping features between the two syndromes include microcephaly, delayed motor development, hypotonia, and failure to thrive.

Conclusion: The stepwise phenotype-first approach is still feasible for limited-resources settings such as Indonesia. Based on this finding, parental examination is granted to confirm possible translocation in one of the parents.

Keywords: 3q28q29 duplication syndrome, chromosomal microarray, Cri-du-chat syndrome, diagnostic approach, global developmental delay, multiple congenital anomalies

17. Differences in Overnight Caregiving Patterns of Mothers and Fathers: Objective Assessment in Two Rare Genetic Syndromes

Presenting Author: Georgie Agar

Agar G.[1,2], Oliver C.[3], Richards C.[3]

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[3] School of Psychology, University of Birmingham, Birmingham, UK

Background: Smith-Magenis syndrome (SMS) and Angelman Syndrome (AS) are associated with elevated rates of poor sleep and behaviours that challenge. These clinical concerns are typically understood from an operant perspective and have a significant impact on caregivers. Both groups show high levels of social approach behaviour and children with SMS demonstrate preference for a particular caregiver. However, it is not yet clear whether this phenotypic preference results in one particular caregiver attending to the child overnight. This study is the first to evaluate phenotypic preferences in social interaction overnight, and how these differ between mothers and fathers.

Methods: Nineteen children aged 4-15 years (8 with AS, 11 with SMS) took part in a week-long at-home assessment of sleep and overnight parent-child proximity. Sleep parameters were recorded using the Philips Actiwatch 2 and proximity data were recorded using custom-built radio frequency identification watches. Standardised definitions of 'wake' and 'interaction' were applied to analyse the number of actigraphy-defined wakings which resulted in an objectively-defined episode of parent-child interaction.

Results: Relative risk analyses found no significant risk of having proximal episodes with the same parent overnight. The primary caregiver was present in the majority of settling episodes in the SMS group but not in episodes which occurred at waking and non-waking, suggesting children with SMS are not more likely to seek out their primary caregiver overnight. In the SMS group, mothers were involved in proximal episodes more frequently than fathers, even when fathers identified as the primary caregiver. In the AS group, mothers' and fathers' involvement was more equal.

Conclusion: Important syndrome differences were identified when examining the role of mothers and fathers in overnight interactions. The majority of proximal episodes in the SMS group involved the mother. These differences in parental involvement have implications for sleep interventions to support the whole family.

Keywords: Sleep, Smith-Magenis syndrome, Angelman syndrome, caregiver, interaction

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Abstracts for Research Symposium 6th – 7th September *(in order of presentation)*

18. KEYNOTE - THE TOM OPPÉ DISTINGUISHED LECTURE: Adapting and Innovating: A Model of Autism Care for Low Resource Settings

Presenting Author: Gauri Divan

***Divan G.*[1]**

[1] *Child Development Group, Sangath, India*

This lecture will describe the journey taken by Sangath, a not-for profit in India, to realize the goal of universal health care for children with autism in low-resource settings that have limited specialty services. Sangath started as a child development centre in Goa, a western state of India, designing its services as a traditional multi-disciplinary team based on traditional high-income country models of ideal care. The early experiences of clinicians and families pushed the team to consider how they could enhance the coverage of evidence-based interventions in the context of the many barriers to centre based models of care. Sangath then began a journey to understand these barriers of access by iteratively adapting, expanding and evaluating a multi-component parent-mediated communication intervention which could be delivered in community settings by non-specialist providers. This body of work has set the stage for a major initiative to scale-up the intervention in the entire region, guided by the principles of universal health coverage for young children with autism. The approach is an example of innovations to expand access to evidence based care for the large majority of the world's children who are currently unreached

19. Targeting Intolerance of Uncertainty in Young Children Diagnosed with Autism: A Randomised Controlled Trial of a Parent-Mediated Group Intervention

Presenting Author: Gail Alvares

Ong C.S.Y.[1,2], Rodgers J.[3], Cooper M.N.[1], Dempsey Z.[1], Kuzminski R.[1], Magiati I.[2], Maybery M.T.[2], Uljarevic M.[4], Whitehouse A.J.O.[1], ***Alvares G.A.[1]***

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[3] *Population Health Sciences Institute, Newcastle University, United Kingdom*

[4] *Department of Psychiatry and Behavioural Sciences, Stanford University, USA*

Background: Young children diagnosed with autism experience high rates of co-occurring anxiety, with uncertainty-related concerns commonly reported. This randomised controlled trial investigated an eight-week parent-mediated group anxiety intervention, 'Coping with Uncertainty in Everyday Situations' (CUES-Junior©).
Methods: Parents of 4 – 7 year-old children diagnosed with autism and experiencing uncertainty-related anxiety were recruited. The primary outcome was change from baseline in blinded assessor ratings of child responses to uncertainty and impact on family, measured post-intervention and two-month follow-up. Secondary outcomes were parent-reported child anxiety and intolerance of uncertainty (IU), parental IU and mental health, parenting sense of competence, along with intervention feasibility and acceptability.
Results: Sixty-four children were randomised to CUES-Junior© (n=33) or waitlist (*n*=31); five families withdrew post-randomization. Immediately post-intervention, significantly more CUES-Junior© participants were rated as clinically improved from baseline in child responses to uncertainty (OR=34.48; 95% CI=1.72-690.04, *p*=.02) and in family impact (OR=8.99; 95% CI=1.52–53.05, *p*=.02) compared to waitlist. Significant improvements were also observed in parent-reported child IU and parenting satisfaction, favouring CUES-Junior©. At subsequent two-month follow-up, CUES-Junior© participants showed sustained improvements in the impact of uncertainty on children, and parental ratings of child IU and anxiety, parenting sense of competence, and parental stress, compared to baseline. The program was feasible to administer and acceptable to parents.
Conclusion: CUES-Junior© had an immediate treatment effect on child responses to uncertain situations and impact on families, with maintained improvements observed at follow-up. This novel mechanism-targeted and autism-informed program holds promise for addressing early uncertainty-related anxiety in young children diagnosed with autism.

Keywords: Autism, anxiety, intolerance of uncertainty, parent group, clinical trial

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20. Anxiety and Challenging Behaviour in Rare Neurodevelopmental Disorders (NDDs): A Focus on DDX3X-Related NDD and CASK-Related NDD

Presenting Author: Jessica Martin

Martin J.A.[1], Mavrogalou-Foti A.P.[1], Eck J.[1], Baker K.[1]

[1] MRC Cognition and Brain Sciences Unit, University of Cambridge, UK

Background: Mental health (MH) symptoms, specifically anxiety and challenging behaviour (CB, including self-injury and aggression), are highly prevalent in children and young people (CYP) with rare neurodevelopmental disorders (NDDs). Improvements in genomic testing have led to increased identification of rare, monogenic, X-linked causes of NDD. Currently, MH symptoms are poorly understood in these conditions. This study aimed to describe anxiety and CB in CYP with *DDX3X*-related NDD and *CASK*-related NDD, two exemplar X-linked conditions that predominately affect females, and explore whether these symptoms are condition-specific, or expected for the severity of developmental delay.

Methods: Parents completed a battery of questionnaires designed for NDD populations, including three assessments of anxiety, and an in-depth measure of CB. Summary statistics will be compared between groups, and to individuals with other heterogeneous, monogenic causes of NDD. A network approach will also be employed to examine within-group associations between MH symptoms, adaptive behaviour and autism-related characteristics. Network properties will then be compared between groups to explore whether symptom-level relationships are influenced by specific diagnosis.

Results: From previous literature, we expect to find heightened anxiety and self-injury in *DDX3X*-related NDD, as well as *DDX3X*-specific associations between MH symptoms, adaptive behaviour and autism-related characteristics. We have no specific predictions for the *CASK*-related NDD group as this is the first systematic exploration of MH symptoms in this condition.

Conclusion: Describing anxiety and CB in these conditions will further our understanding of MH symptoms in *DDX3X*-related NDD and *CASK*-related NDD. Results may be relevant to the broader population of CYP with rare NDDs, and potentially lead to earlier identification and pro-active support for young people and their families.

Keywords: Mental health, anxiety, challenging behaviour, X-linked neurodevelopmental disorder, network approach

21. Correlation Between Uncertainty and Anxiety in Parents of Children with Down Syndrome in a Developing Country: A Cross-Sectional Study in Indonesia

Presenting Author: Irene Astrid Larasati

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Background: A previous study revealed that uncertainty experienced by caregivers of paediatric with chronic diseases correlated with increased psychological distress, including anxiety. The purpose of this study is to ascertain whether anxiety and uncertainty are correlated in Indonesian parents of children with Down syndrome (DS).
Methods: A cross-sectional study was conducted among 126 parents (54 fathers and 72 mothers) of children with DS from two hospitals in Central Java, Indonesia. Parent's uncertainty was measured using Indonesian version of the Parent's Perception of Uncertainty Scale (I-PPUS) while Hamilton Anxiety Rating Scale (HAM-A) was used to measure parent's anxiety. The Spearman's rank test was applied to analyse the relationship between parents' uncertainty towards illness and anxiety. Factors associated with uncertainty were analysed using an independent t-test.
Results: Majority (86.5%) of the parents of children with DS have a low level of anxiety, interestingly the level of anxiety was weakly correlated with the parent's uncertainty ($p<0.001$; $r = 0.314$). The mean PPUS score of parents of children with DS was 63.3±9.32. Fathers had a significantly higher uncertainty score (65.1±9.32) compared to mothers (61.8±9.13) ($p = 0.027$).
Conclusion: Uncertainty experienced by the parents of children with DS significantly correlated with anxiety pertinent to their DS children's conditions. Healthcare providers should be aware of offering support and related information about DS children's treatment, prognosis, and health to manage the anxiety level of the parents especially father in order to reduce the parents' uncertainty levels.

Keywords: Down syndrome, uncertainty, anxiety, parents, developing country, Indonesia

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22. THE LECLEZIO-DE VRIES PRIZE: Recognizing Anxiety in Turner Syndrome Early: Community Engaged Development of a Patient-Centered Outcome Measure

Presenting Author: Talia Thompson

Thompson T.[1,2], Carl A.[1], Klamut N.[1], Good M.[3,4], Haag E.[3], Swain D.[1,2], Maugel L.[3], Masters M.[3], Davis S.[1,2]

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[2] *Children's Hospital Colorado, USA*

[3] *Turner Syndrome Colorado, USA*

[4] *Turner Syndrome Global Alliance*

Background: Turner syndrome (TS), caused by complete or partial loss of the second X chromosome, affects 1 in 2,000 females. The TS community ranks anxiety as a top research priority and our previous work shows unique triggers and symptomatology in TS. A lack of validated anxiety screening instruments in TS prohibits timely and accurate diagnosis, as shown by documented under-ascertainment of paediatric anxiety disorders in TS. Further, clinical trial readiness for anxiety interventions in TS requires clinically valid outcome measures. This study aimed to tailor an existing paediatric anxiety screener for TS.

Methods: Two rounds of cognitive interviews were conducted with N=10 TS patients/caregivers to assess comprehension, identify problematic questions, and elicit suggestions for improvement. We partnered with our existing community advisory board (CAB; 2 patients, 4 parents, 2 clinicians) to systematically adapt the screener to improve fit, feasibility, and acceptability for TS. We are actively recruiting participants (current N=84) for a rigorous psychometric evaluation of a newly developed measure: RATE (Recognizing Anxiety in Turner syndrome Early). Final results are expected end of summer, 2024.

Results: Cognitive interview data coalesced around three themes: 1) Comprehension Challenges, 2) Unclear Response Options, 3) Limited Applicability for TS. Qualitative findings indicated that the un-adapted screener may underestimate anxiety in TS. CAB adaptations included editing problematic words, clarifying the Likert scale, and adding a "TS Health Anxiety" subdomain. After adaptations, round two cognitive interviews showed improved acceptability and understanding. Preliminary quantitative data show >70% positive screens (total score ≥25) for both child and parent forms. We will present reliability (internal consistency, test-retest reliability) and validity (correlations to gold standard measures and clinical interviews) results at the fall conference.

Conclusion: After further validation, RATE can be used to screen for anxiety in TS clinical settings and as a patient-centred outcome measure for future clinical trials.

Keywords: Turner Syndrome, anxiety, screening, patient-centred outcome measures

23. A Caregiver-Reported Profile of Separation Distress and Attachment-Related Behaviours in Angelman Syndrome

Presenting Author: Effie Pearson

Pearson E.[1], Roberts R.[1], Waite J.[1], Oliver C.[2]

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

[2] School of Psychology, University of Birmingham, UK

Background: There are early reports of elevated rates of separation distress in Angelman syndrome (AS). Heightened social drive, particularly towards caregivers, has been linked to the genetic basis of AS and may be directly associated with separation distress in this population. However, this is yet to be explored. Two studies were conducted to characterise separation distress in AS, by describing responses to separation from a caregiver, the relation to elevated social motivation and the impact of attachment-related behaviours.

Methods: A 25-item semi-structured clinical interview and 13-item questionnaire were developed based on previous measures, literature reviews and Patient Participant Involvement. *Questionnaire study:* Thirty-seven caregivers of people with AS (*Mage* = 24.5, SD =11.3) completed the questionnaire. Questions explored the frequency, severity and presentation of distress in six situations where separation occurs. *Interview study:* Interviews were completed with 26 main caregivers of people with AS (*Mage* = 24.5, SD =12.26). Interview questions explored social motivation, attachment-related behaviours, and responses to separation, with profiling of separation distress when appropriate.

Results: *Questionnaire study*: 54.1% (n=20) respondents reported moderate to extreme distress more than half of the time, in at least one situation when separating from a main caregiver. Frequently endorsed behaviours during separation-related distress were negative vocalisations/affect (48.4%), appearing worried/anxious (45.2%), and proximity-seeking (41.9%). *Interview study*: Content analysis identified descriptions of social preference, proximity-seeking behaviour, and responses to separation in Angelman syndrome. The influence of age, genetic mechanism, and ability were also explored, alongside caregiver perceptions of the impact of these behaviours on wellbeing.

Conclusion: Results suggest separation distress has a significant impact on people with AS and their caregivers. Results will be discussed in the context of the behavioural phenotype and genetic basis of AS, alongside implications for support for people with AS and their families.

Keywords: Angelman syndrome, separation distress, behaviour, social motivation, genetic syndrome, measure development

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24. Psychopathology, Cognition and Developmental Coordination Disorder Associated with 15q11.2 Deletion

Presenting Author: Jessica Hall

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Background: High rates of neurocognitive and psychiatric problems have been reported in children with 15q11.2 deletion in population-based studies, however currently this copy number variant (CNV) is considered to be "pathogenic of mild effect size". There remains a lack of studies within samples representative of a clinical population, and in children. This work aims to investigate the prevalence of psychiatric disorders, developmental coordination problems, and neurocognitive impairment in a clinical sample of children with 15q11.2 deletion, compared to sibling controls, and to investigate the relationship between intelligence quotient (IQ) and psychopathology, and IQ and motor problems.

Methods: Cognitive performance, developmental coordination problems, and psychopathology were assessed in 50 children with 15q11.2 deletion recruited using a genotype-first approach (80% male, mean age 9.8, SD=3.1) and 150 unaffected controls (80% male, mean age 10.4, SD=2.8). Psychopathology was assessed by Child and Adolescent Psychiatric Assessment (CAPA) and Developmental Coordination Disorder (DCD) by the Developmental Coordination Disorder Questionnaire (DCDQ). Cognition was assessed using the Weschler Abbreviated Scale of Intelligence (WASI) and the Cambridge Neuropsychological Test Automated Battery (CANTAB).

Results: Children with 15q11.2 deletion had more diagnoses of, and more severe symptom counts for ADHD, Anxiety, ODD and Autism, greater prevalence of DCD and decreased cognitive ability across all domains. There was no relationship between cognitive performance and psychopathology, however, lower Full Scale IQ and Performance IQ scores were associated with increased motor coordination problems.

Conclusion: Children with 15q11.2 deletion have neurocognitive impairment, increased developmental coordination difficulties, and greater levels of psychopathology compared with controls. These findings suggest that 15q11.2 deletion has pleiotropic effects. This study highlights the need for clinicians to be aware the potential psychiatric, cognitive and developmental coordination implications of children with a diagnosis of 15q11.2, in order to aid access to early intervention.

Keywords: 15q11.2 deletion, Copy Number Variant (CNV), genetics-first, cognition, developmental coordination disorder, psychiatric diagnosis

25. KEYNOTE: The Role Of Genomic Counselling And Public Health Genomics In Low and Middle Income Countries in the Asia-Pacific Region

Presenting Author: Thong Meow-Keong

***Thong M-K.*[1,2]**

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In 2015, the 2030 Agenda for Sustainable Development Goals (SDG 2030) were adopted with 17 sustainable development goals as its targets (United Nations, 2017). The focus is on continuing the progress made in Millenium Development Goals (MDGs) as well as to reduce non-communicable diseases (NCDs). This focus on NCDs meant that congenital disorders and genetic conditions will be included for prevention and control globally. In particular, the SDG 3 included targets to end preventable deaths of newborns and children under 5 years of age by 2030, provide universal health care coverage and reduction of premature mortality from NCDs by 33% as well as support the development and research for medicines for both communicable and NCDs. These new targets meant that both curative and preventive strategies are needed to prevent congenital disorders. The World Health Assembly reported concerns that birth defects were not recognized as a priority in public health (World Health Assembly, 2010). In the post-COVID pandemic era, there are genuine concerns the rate of progress in many areas is far slower than needed to meet the targets by 2030. Some of the issues identified that needed urgent attention included the need to improve healthcare data quality, reducing inequalities within and among countries, renewed efforts to reduce infant mortality rate and to address a critical shortage of skilled manpower and healthcare funding. Genomic counselling and public health genomics have been identified as preventive strategies with an important role to play in low- and middle-income countries in helping to reduce the inequities encountered for rare diseases and congenital disorders.

26. APOε and KLOTHO Gene Variants Do Not Affect Diagnosis and Severity of Fragile X-Associated Tremor/Ataxia Syndrome Phenotypes

Presenting Author: Tri Indah Winarni

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Background: FXTAS, is a late-onset of progressive neurodegenerative disorder, characterized by intention tremor, gait ataxia, executive function deficits, and brain atrophy. The penetrance in older adults premutation males is higher (47%-75%) compared to females (16%). *APOe4* allele is the strongest genetic risk factor for cognitive impairments in all ethnic groups, in contrary *KLOTHO* variants acts as a protector of cognitive impairments called as longevity. This study investigated the potential role and interaction of the APOe and KLOTHO genes on the penetrance of Fragile X-associated tremor/ataxia syndrome (FXTAS) and on the IQ trajectory.

Methods: FXTAS was diagnosed based on molecular, clinical and radiological criteria. Single nucleotide polymorphism (SNP) genotyping was carried out for *APOe* and *KLOTHO* using Real Time PCR. The cognitive assessment (VIQ, PIQ, and FSIQ) based on standardized testing was administered in 73 PM males (65 with and 8 without FXTAS) on the first and subsequent visit.

Results: Males with the premutation (PM) over 50 years, 165 with and 34 without FXTAS diagnosis, were included in this study and were compared based on their *APO (e2-e3-e4)* and *KLOTHO* variant (*KL-VS*) genotypes. The effect of *APOe4* on FXTAS stage and on diagnosis did not differ significantly by *KL-VS* genotype with interaction effect P = 0.662 and P=0.91, respectively. A larger decline in Verbal IQ (VIQ) in individuals with an *APOe4* allele compared to those without an *APOe4* allele (P = 0.04) was found in the individuals with an *APOe2* allele.

Conclusion: The *APOe4* and *KL-VS* genotypes do not appear to predispose to either FXTAS diagnosis or stage in male carriers of the PM allele. A further study is needed to establish the trend of IQ decline in the individuals who carry *APOe4* with *APOe2* compared to those without APOe4.

Keywords: FMR1 gene, FXTAS, premutation, KLOTHO, APOε4

27. Clinical Phenotype and Altered Metabolomic and Proteomic Profiles in Individuals with 22q11.2 Deletion Syndrome

Presenting Author: Flora Tassone

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Background: Chromosome 22q11.2 deletion syndrome (22q) displays extreme phenotypic heterogeneity and represents the strongest known molecular genetic risk factor for psychosis and schizophrenia. Thus, it is a strong and unique model for prospective study of risk and protective factors for psychosis, as many at-risk youths can be studied even before symptoms appear. The well-defined microdeletion contains multiple genes which haploinsufficiency has the potential of altering protein and metabolic profiles which could identify endophenotypes among those with 22q and represent predictors of psychosis diagnosis even before symptoms appear.

Methods: Leveraging on the unique data and specimens collected from individuals with 22q followed longitudinally we performed untargeted metabolic and proteomic analysis in plasma samples derived from 30 subjects (22q n=16, TD n=14) with and without medical involvement, psychiatric conditions, and ASD. Deletion size was characterized by ddPCR.

Results: We observed a large number of metabolites showing significant changes in expression levels in 22q as compared to TD, including taurine and arachidonic acid, which play a central role in neurodevelopment. In addition, significant changes were detected in the expression of several proteins including those involved in biological pathways such as gene expression, the PI3K-Akt signalling pathway, the complement and coagulation cascade and cytokines involved in immunoregulatory functions.

Conclusion: We have characterized a plasma metabolic and protein profile and identified unique biomarkers in 22q which may play a potential role for the onset of the observed 22 q phenotypes. The altered protein pathways in 22q may provide insights of the biological mechanisms underlying the neurodevelopmental phenotype and could be used as markers of prognosis, disease development and progression. Finally, they may provide missing molecular outcome measures to assess early-diagnosis treatment and the efficacy of response to future pharmacological interventions.

Keywords: psychosis, omics, 22q deletion syndrome, neurodevelopment

28. Transcriptomic Signatures in Blood and Brain Related to Intellectual Functioning and Behavioural Features of Prader-Willi Syndrome

Presenting Author: David Godler

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Background: This study defined gene expression changes found consistently in all cell types in the prefrontal cortex (PFC) of donors with Prader-Willi syndrome (PWS) as compared to controls and examined relationships between these changes in blood and clinical severity.

Methods: 8,338 long non-coding RNAs and 17,079 protein-coding genes were examined using single-nucleus RNA-sequencing in the PFC of 8 donors with PWS (4 15q11-q13 deletion and 4 non-deletion genetic subtypes) and 4 age- and sex-matched neurotypical controls. The shortlisted differentially expressed genes (DEG) were examined using droplet digital PCR (ddPCR) in peripheral blood mononuclear cells (PBMCs) from an independent cohort of 38 individuals with PWS (16 deletion and 22 non-deletion), aged 1 to 45 years, with mRNA levels related to: (i) intellectual functioning assessed using the Mullen Scales of Early Learning or an age-appropriate Wechsler Scale; (ii) challenging behaviours assessed using the PWS Behavioral Questionnaire; and (iii) autistic traits using the Autism Diagnostic Observation Schedule-2nd Edition.

Results: 54 genes and related pathways were consistently dysregulated across all cell types in the PFC of the PWS group compared to controls, with *RPS18* being the only protein coding gene upregulated in PWS PFC across all comparisons. Increase in *RPS18* mRNA in PBMCs was associated with intellectual functioning and challenging behaviours, but not autistic traits in children with PWS (<13 years old).

Conclusion: If confirmed in future studies, these findings may lead to development of new prognostic markers and tests utilizing peripheral tissues, and therapeutics targeting the genes and related pathways consistently dysregulated between brain and peripheral tissues.

Keywords: RPS18, Prader-Willi syndrome, behavioural issues, intellectual functioning, brain transcriptomics

29. KEYNOTE: Interventions for Families with People with Developmental Disabilities in Low and Middle Income Countries and Remote Areas

Presenting Author: Stewart Einfeld

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We will review the research published in this field in the last 12 years following our previous review in 2012. Also, we will discuss projects designed to include people with disabilities in planning for natural disasters in Indonesia and the Pacific. Finally, we will discuss work undertaken to provide parent training for children with disabilities in remote parts of Australia.

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30. KEYNOTE: A Promising New Treatment for Fragile X Syndrome

Presenting Author: Randi Hagerman

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Background: Metformin, originally derived from the French Lilac plant, has a long history of medicinal use dating back to ancient Egypt. In the mid-20th century, it became established as a treatment for diabetes. Preclinical studies of metformin treatment in the KO mouse and Drosophila model reversed the fragile X phenotype and normalized the upregulation of the mTOR pathway.

Methods: Metformin was administered to individuals with FXS, including those with the Prader-Willi phenotype. Behavioural improvements were observed in 7 patients, and parents reported enhanced conversational language. Further case studies indicated cognitive improvements and prevention of macroorchidism with metformin use prior to puberty. Two open label studies of metformin in FXS demonstrated improvements in behaviour and development in one and improvements in TMS studies in another. The results of a RCT at 3 sites lasting 4 months and enrolling 108 patients will be presented. The RCT was followed by an open label study and the first 26 patients were followed for 1 to 3 years with the Leiter 3 and the Vineland III at baseline and at follow-up.

Results: The results demonstrated that both the Leiter 3 and the Vineland III were stable in follow-up without the significant cognitive decline that has been typically seen in those with FXS who are followed through childhood and adolescence. Additionally, recent studies in KO mice treated with metformin after birth demonstrated greater gains than those treated later in development. These results underscore the potential benefits of early intervention, advocating for future research in younger children under 6 years.

Conclusion: In conclusion, metformin shows promise as a treatment for FXS, with ongoing and future longitudinal studies necessary to fully elucidate its long-term benefits. Currently, metformin is available for off-label use in individuals with FXS, offering a potential therapeutic avenue pending further validation.

Keywords: Metformin, Treatment, Cognition, Fragile X syndrome, Controlled Trial

31. What Can We Learn About Health and Healthcare From Large-Scale, Routinely-Acquired Data in the United Kingdom: Studies in Fragile X Syndrome

Presenting Author: Andrew McKechanie

McKechanie A.G.[1,2,3], Stanfield A.C.[1,2,3], Fisher L.[4], Morgan C.L.I.[4], Jones B.I.[4], Cooper A.[5], Conway P.[5]

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Background: Many studies examining epidemiology and health of individuals with rare genetic conditions or behavioural phenotypes rely on cohorts acquired by individual clinicians or centres. This ensures high quality data can be collected, but often at the expense of the statistical power that can be brought by being able to look at larger cohorts. In this series of studies, we used large-scale, routinely-acquired healthcare data from England to examine questions relating to pre-diagnostic healthcare, epidemiology, healthcare utilisation and mortality in fragile X syndrome (FXS) in larger samples than is often possible.

Methods: We used linked data from the Clinical Practice Research Datalink (CPRD) Aurum database which contains longitudinal (30+ year) data on ~38 million patients and linked data from the Hospital Episodes Statistics and Office for National Statistics (ONS) mortality datasets. Cases were selected if they had ≥1 medical code indicative of FXS. Patients with FXS were matched on a 1:1 ratio to non-FXS controls on age, gender and practice for the case-control comparisons.

Results: The highest observed prevalence of FXS across age groups was ~1/2400 for males ~1/6900 for females. We estimated that the prevalent population of individuals with a FXS diagnosis in the UK is 6835, with a further 9639 being not yet diagnosed. Prior to diagnosis, individuals with FXS had significantly more diagnoses of learning disability, autism, seizures, gastrointestinal problems, and otitis media and had higher numbers of healthcare contacts in all settings (primary care, in-patient, out-patient and Accident & Emergency) than controls. Compared to matched controls, individuals with FXS had a significantly higher risk of death (Hazard Ratio 2.20) and a mean of 10 life-years lost.

Conclusion: The use of large-scale, routinely-acquired data can provide insights into the health and healthcare of individuals with fragile X syndrome. This approach should be considered in other genetic conditions.

Keywords: Fragile X Syndrome, Data Linkage, Epidemiology, Healthcare Utilisation, Mortality

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32. Exploring Electroretinogram (ERG) Alterations as a Novel Biomarker for Fragile X Syndrome: Comparative Analysis of ERG and FMRP Levels among Full Mutation, Premutation, and Healthy Controls

Presenting Authors: Hazel Maridith B. Biag & Ellery Santos

Biag H.M.B.[1,2] / Santos E.R.[1,2], Hasan H.[2,3], Randol J.L.[4], Hwang Y.H.[4], Schneider A.[1,2], Tassone F.[2,4], Hagerman P.[4], Hagerman R.J.[1,2]

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Background: Fragile X Syndrome (FXS) is caused by suppression of the Fragile X Messenger Ribonucleoprotein 1 (*FMR1*) gene, leading to a lack of the encoded protein, Fragile X Messenger Ribonucleoprotein (FMRP). FMRP is expressed in various layers of the retina. Altered b-wave amplitude, measured via the electroretinogram (ERG), has been observed in both the mouse models of FXS and in individuals with FXS. The purpose of this study was to investigate ERG differences in those with full mutation FXS and compare them to premutation (PM) carriers, and healthy controls (HC). Additionally, it aimed to establish correlations between ERG findings and FMRP expression in the blood.

Methods: Electroretinograms and FMRP blood levels were collected for 23 full mutation FXS (n=13 males, n=10 females), 27 premutation carriers, and 19 healthy controls. The ERG protocol included the following: flash - 30 white flashes at a 2Hz interval, flicker - a series of repeated flashes at 28.3Hz, and Photopic Negative Response (PhNR) - 3.4Hz red flashes presented against a blue background. FMRP levels were measured by FRET analysis. Statistical analyses were conducted to correlate ERG results and blood FMRP levels.

Results: Statistically significant differences were found in the ERG PhNR response for FXS males, compared to PM carriers, HC, and females with FXS. Analyses for FMRP levels in the blood showed noteworthy distinctions between FXS males and carriers of the PM and HC. Lastly, preliminary analyses between ERG b-wave amplitude and FMRP blood levels showed significant association within the FXS cohort and the HC group. In progress analyses, including ERG/FMRP correlations to IQ, will be presented at the conference.

Conclusion: This study highlights ERG/FMRP differences in those with FXS, PM, and HC. Furthermore, the correlation between ERG findings and FMRP blood levels underscores the potential utilization of ERG as a biomarker for FXS.

Keywords: Fragile X Syndrome, Pre-mutation Carrier, Electroretinogram, FMRP blood levels

33. FORWARD 2011-2020 Cohort: Frequencies of Non-Drug Services in Individuals With Fragile X Syndrome With and Without Co-occurring Autism Spectrum Disorder

Presenting Author: Dejan Budimirovic

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Background: Individuals with fragile X syndrome (FXS) are often co-diagnosed with autism spectrum disorder (ASD), requiring a variety of non-pharmacological treatments. Yet, the valuable applied behaviour analysis (ABA) intervention appears to be underused in individuals with FXS based on the FORWARD (Fragile X Online Registry with Accessible Research Database) 2012-2014 data on (n=~600/713) subjects with FXS eligible for ASD-related analyses. This study aims to investigate the utilization of the above services in FXS using a larger longitudinal clinic-based dataset.

Methods, Results, Conclusion: We will use data from the large molecularly confirmed FXS (n=1,834) longitudinal FORWARD project, collected during 2011–2020 at 26 FXS Clinics in the USA. The vast majority (n=1,458, 79.5%) of the participants have at least one parent and one clinician form and are eligible for the study. We will examine cross-sectional frequencies of parent-reported non-pharmacological services as a function of clinician-based ASD status by analysing individuals that had both parent- and clinician-reported data from their last time point in the data collection. ASD diagnosis was based on DSM-5 criteria assessed during clinical evaluations. The types of services will include early intervention, ABA, speech-language (SLT), occupational (OT) therapies, and other modalities provided to age groups 0-3 years, preschool, and school-age. Statistical analyses will be performed using SPSS. Demographic features of the cohort included 75.8% males (n=1,390) and 73.2%White (n=1,342). In the subset of participants with at least one parent and one clinician form, 51.5% (=751/1458) had a previous or current diagnosis of ASD.

Among the males, 58.2% (=644/1107) had a diagnosis of ASD whereas only approximately one-third of the females 30.3% (=105/347). Overall, the cohort is large enough to accomplish the proposed analyses, including frequencies of ABA services over time through the different age groups. Analyses will be presented at the conference.

Keywords: fragile X syndrome, autism spectrum disorder, FORWARD study, non-pharmacological treatments

34. KEYNOTE: Global Insights on Screen Media Exposure and 'Virtual Autism': Exploring the Link

Presenting Author: Weerasak Chonchaiya

***Chonchaiya W.*[1]**

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There is growing evidence across many countries that young individuals with autism spectrum disorder (ASD) are frequently exposed to electronic screen media from an early age and spend more time on media compared to their peers. Increased screen time has been shown to be correlated with greater severity of ASD and lower developmental quotients. Additionally, atypical changes in the functional connectivity of various intra- and inter-brain networks were also observed in those with ASD with prolonged use of screen media. Recent research also indicates that individuals with a higher ASD polygenic risk score tend to have longer screen time. On the contrary, early exposure to screen media during infancy has been associated with ASD-like symptoms or a diagnosis of ASD during the preschool years. Clinical observations suggest that reducing inappropriate screen media exposure, in conjunction with standard behavioural and early interventions, can improve developmental and behavioural outcomes in young individuals with ASD or ASD-like behaviours. However, further research is needed to fully understand the relationship between screen media exposure and ASD. Raising awareness among parents, especially those from high-risk or disadvantaged backgrounds, about the potential risks of exposure to early and excessive screen media on child development and behaviours is crucial. Implementing practical strategies to optimize screen media use may mitigate the adverse effects of inappropriate and excessive screen media exposure on child developmental outcomes. Furthermore, this presentation will discuss the advantages and disadvantages of using the term "virtual autism" in clinical practice, with a particular focus on the context of Thailand.

Keywords: Autism, behaviour, development, electronic screen media, virtual autism

35. Neurodevelopmental and Facial Phenotype and MRI Findings in a Cohort of Early School-Aged Children with Low-Moderate Prenatal Alcohol Exposure

Presenting Author: Elizabeth Elliott

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Background: High level prenatal alcohol exposure (PAE) can cause a spectrum of neurodevelopmental impairments, structural brain abnormalities, and facial dysmorphology, including Fetal Alcohol Spectrum Disorder (FASD). Over 60% of pregnant women consume some alcohol, especially before pregnancy awareness, and a proportion continue throughout pregnancy, albeit at lower levels. Robust evidence is needed to assist pregnant women to make informed choices about alcohol. The aim of this study was to examine outcomes following low-moderate PAE and provide convincing evidence to inform a women's decision to drink alcohol or abstain.
Methods: The Asking Questions about Alcohol in Pregnancy (AQUA) study (Melbourne, Australia), is a community-representative cohort of 1570 mother-child pairs, designed to collect high-quality data on PAE, relevant confounders, and neurodevelopmental and physical outcomes in offspring with low-moderate PAE. Between 2018 and 2020, children aged 6-8 years were comprehensively examined for neuropsychological functioning (n=696), facial dysmorphology (n=363) and brain structure/function (n=143).
Results: No meaningful relationships were found between low-moderate PAE and neuropsychological functioning. 3D imaging provided evidence for an effect of PAE on the shape of the eyes and nose, whether exposure occurred only in trimester one or throughout pregnancy. Features were not congruent with those seen in a comparison sample of children with FASD. Brain MRI analysis revealed reductions in the right caudal anterior cingulate cortex volume and area and right cingulum tract cross-sectional area following low-moderate PAE throughout gestation.
Conclusion: Subtle changes in facial shape and brain structure support a biological effect of low-moderate PAE throughout gestation on fetal development. The teratogenic vulnerability of the face and brain is not however reflected in measurable neurodevelopmental impairment in early school-aged children following low to moderate PAE. New research is needed to examine the complex relationships between the dose and timing of PAE and the consequences of exposure at all developmental levels.

Keywords: Fetal Alcohol Spectrum Disorder (FASD), Prenatal Alcohol Exposure (PAE), neurodevelopment, teratogenicity

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36. KEYNOTE: Genetic Therapies to Target Disease Defects in Neurodevelopmental Disorders

Presenting Author: Elizabeth Berry-Kravis

***Berry-Kravis E.*[1]**

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The last decade has seen significant advances in identification of genes causing neurodevelopmental disorders (NDDs) and improved diagnosis of patients in clinic. Now that the cause of these disorders is increasingly understood, therapies to target the underlying genetics are being employed and are in early trials. These therapies include gene therapy, antisense oligonucleotides (ASOs) and even gene editing. Currently gene therapy is in early phase trials for Rett syndrome and will soon be in trials for Phelan-McDermid syndrome. There is preclinical work toward gene therapy for fragile X syndrome, Angelman syndrome and other NDDs. ASOs that produce a genetic correction of disease are in trials for Angelman syndrome, SCN1A, SCN2A, and have been proposed for fragile X syndrome, PACS1 syndrome, MEF2C syndrome and others< Although these potentially life changing treatments are now becoming a reality, there are still many issues and questions regarding how well they can reverse disease and how to best deliver these agents to the brain. Issues like route of delivery, brain penetration and fractions of neurons targeted, amount of protein produced and regulation of the amount of protein within neurons, protection from immune reactions to the delivery vector and the protein being expressed, and how well any given genetic neurological disease can be corrected at various ages of treatment. This presentation will discuss these issues as well as present early efforts toward therapies that provide genetic correction of the underlying disease in NDDs.

37. Presence and Severity of Challenging Behaviours in SYNGAP1-Related Intellectual Disability

Presenting Author: Sydni Weissgold

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Background: Clinical case series of SYNGAP1 (a non-inherited intellectual disability (ID)) have highlighted widespread prevalence of challenging behaviours (CB), such as self-harm and physical aggression. This study, an ongoing natural history study of behaviour in SYNGAP1, aims to describe in detail the range and severity of CB in SYNGAP1-related ID.

Methods: The Challenging Behaviour Interview (CBI), a 2-part informant-report interview which examines the presence and severity of a series of CBs, was administered to caregivers of individuals with SYNGAP1 (N = 13; 38% male; mean age = 8 years) and typically developing controls (TDC) (N = 11; 45% male; mean age = 10 years). Responses were scored on Likert scales; severity scores were calculated for each category of CB as the sum of the responses (maximum score for each category of CB = 43).

Results: The results show that 100% of participants with SYNGAP1 demonstrated CBs, including physical aggression (77%), stereotyped behaviour (69%), self-injury (62%), pica (23%), inappropriate removal of clothing (23%), inappropriate vocalizations (23%), destruction of property (23%), verbal aggression (15%), stealing (15%), self-induced vomiting (15%), and smearing (8%). 18% of TDC displayed challenging behaviours.

Physical aggression (X^2 (1) = 8.48, p = 0.004), stereotyped behaviours (X^2 (1) = 9.41, p = 0.002) and self-injury (X^2 (1) = 7.57, p = 0.006) were statistically significant in SYNGAP1 in comparison to TDC. For individual CBs, the median severity scores were highest for self-injury (median = 24.9), verbal aggression (median = 24.5), physical aggression (median = 23.0), inappropriate removal of clothing (median = 22.0) and smearing (median = 22.0).

Conclusion: This examination demonstrates the variety in types of CBs present in SYNGAP1 and identifies that physical aggression and self-injury behaviours are both common and severe. Ongoing work will determine how CBs relate to participant characteristics, such as developmental level and sensory processing.

Keywords: SYNGAP1, intellectual disability, challenging behaviour

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38. Exploring the Profile of Executive Function Within SATB2-Associated Syndrome to Inform Models of Behavioural Outcomes

Presenting Author: Lauren Shelley

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Background: *SATB2*-associated syndrome (SAS) is characterised by intellectual disability, speech delay, and palatal and dental problems. High rates of behaviours that challenge (BtC; 42-77%) towards others and/or the environment are reported. Recent research suggests these BtC are associated with executive function (EF) difficulties. To further inform models of behavioural outcomes in SAS, this study aimed to 1) examine the profile of EF in SAS compared to autistic individuals with intellectual disability (Aut+ID) and 2) explore age-related changes in EFs within SAS.

Methods: Caregivers of individuals with SAS (n=37; M_{age}=13.75 years) completed the Behaviour Rating Inventory of Executive Function-Preschool Version (BRIEF-P) alongside a measure of BtC frequency and severity. Individuals with SAS (n=35; M_{age}=14.09 years) completed direct EF assessments of inhibition, working memory, and shifting. Associations between BRIEF-P subscales and BtC were examined. Cross-group comparisons were conducted using existing BRIEF-P and EF assessment data from Aut+ID individuals. BRIEF-P data within SAS were explored using a developmental trajectory approach.

Results: SAS and Aut+ID groups had higher BRIEF-P scores compared to typically developing cohorts from the BRIEF-P manual (p<.001). Individuals with SAS showed poorer performance on EF assessments of shifting compared to Aut+ID individuals (p=.001); there were no other significant between-group differences in EF profiles. In SAS, all BRIEF-P subscales were associated with BtC frequency (p<.001), while inhibition (p=.002), emotional control (p=.001), and shifting (p<.001) subscales were selectively associated with BtC severity. EFs of shifting and emotional control emerged as relative strengths within SAS; however, trajectory analyses indicated minimal age-related improvement in these EFs compared to inhibition, working memory and planning/organisation (p<.05).

Conclusion: Findings suggest similar profiles of EF difficulties in SAS and Aut+ID. Longitudinal research is needed to substantiate these cross-sectional findings; however, EFs, particularly shifting and emotional control, are indicated to be important for understanding and supporting behavioural outcomes in SAS.

Keywords: SATB2-associated syndrome, SATB2, Behaviours that challenge, Executive function, Autism, Intellectual disability

39. Significance of Attention Deficit Hyperactivity Disorder (ADHD) Traits in SYNGAP1-Related Intellectual Disability

Presenting Author: Andy Stanfield

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Background: Pathogenic variants in SYNGAP1 have been previously associated with high levels of intellectual disability along with language impairment, autistic traits, attention deficit hyperactivity disorder (ADHD) traits and aggression. Of these, ADHD traits represent perhaps the most amenable target for existing interventions. We therefore set out to examine the extent of ADHD traits in a cohort of individuals with SYNGAP1 and their significance in terms of behavioural challenges.

Methods: Children and young adults with SYNGAP1-related ID were recruited through family support organisations. Each were administered a series of assessments according to their age, including the Achenbach Series of Empirical Assessments (ASEBA), Social Communication Questionnaire and Vineland Adaptive Behaviour Scale. Linear regression was conducted to examine the relationship between the ASEBA aggressive behaviour factor and age, gender, ASEBA 'inattention' and 'anxiety / depression' factors, SCQ score and Vineland Adaptive Behaviour Composite Score.

Results: Thirty-two individuals from the UK with SYNGAP1 were recruited (12M, 20F; mean age 9.7, SD=7.1). Two had pre-existing clinical diagnoses of ADHD, although the mean score on the ASEBA inattention subscale was above the clinical cut-offs: 71.3 (SD+7.6). Inattention scores were not related to overall adaptive behaviour level (rho=-0.176, p=0.34). Linear regression revealed that ADHD traits significantly predicted aggressive behaviour (t=3.20, p=0.004), whereas no significant relationships were seen for age, gender, adaptive behaviour, autistic traits or anxiety / depression.

Conclusion: Despite low levels of clinical diagnosis, ADHD traits in SYNGAP1 are common and are associated with aggressive behaviour. Identifying and treating ADHD traits may be a valuable strategy in reducing aggressive behaviour in children with SYNGAP1-related ID.

Keywords: SYNGAP1, ADHD, aggression

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40. Clinical Characteristics of Creatine Transporter Deficiency (CTD): Final Results of the Vigilan Observational Study

Presenting Author: Judith Miller

Miller J.[1], Farmer C.[2], Blair S.[3], Brandabur M.[3], Porter F.D.[4], Thurm A.[2]

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Background: Creatine Transporter Deficiency (CTD) is a rare disease associated with intellectual disabilities. Results from the four-year Vigilan Observational Study of CTD can help us learn the phenotype and developmental trajectories in this population.

Methods: This study (NCT02931682) used parent questionnaires, clinical assessments, and direct testing to characterize clinical features of males with confirmed CTD (SLC6A8 pathogenic variant) for up to 4 years.

Results: Fifty patients (mean baseline age, 7.6 years; range, 1.5-24.4 years) were enrolled. The most common first symptoms parents recognized (with hindsight) were developmental delays or difficulty feeding/gastrointestinal symptoms/failure to thrive before 12 months, or developmental delays between 12-36 months. Without a known family history, the median age of first symptom in hindsight was 6 months, median age of first evaluation was 15 months, and median age of diagnosis of CTD was 43 months. From parent history and prospective data collection during the study, we tracked whether and at what age participants reached four notable functional milestones (ages of walking, first words, first sentences, toileting skills) or experienced the onset of a seizure disorder. We will also present medication usage, non-pharmacological interventions, and developmental trajectories from standardized developmental testing across the study period. For standardized testing, we also modelled the trajectories seen in our CTD sample in contrast to trajectories expected for children in the general population.

Conclusion: The summary interpretation of observations made provides an important means of evaluating trajectories of developmental disruption associated with CTD, which may improve clinical care as well as research into the impact of possible interventions.

Keywords: Intellectual disabilities, neurodevelopmental, developmental trajectories, Creatine Transporter Deficiency Syndrome

41. Exploring Predictors of 36-month Language and Motor Outcomes in Children Prenatally Diagnosed with Sex Chromosome Trisomy to Inform Early Intervention Trials

Presenting Author: Nicole Tartaglia

Tartaglia N.[1,2], Bothwell S.[1], Janusz J.[1], Ross J.[3], Davis S.[1]

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Background: Increasing practice of prenatal cell free DNA screening has steadily led to increased identification of sex chromosome trisomy (SCT) conditions (XXY/Klinefelter syndrome, XXX, XYY) in neonates. While there is wide variability in SCT neurodevelopmental features, there is a known risk for early speech and motor delays. This project aimed to identify variables in the first 12 months of life associated with speech and motor abilities at 36 months of age.

Methods: The eXtraordinarY Babies Study is a prospective study of health and neurodevelopment in children with prenatally identified SCT. Participants enrol between 2–12 months of age and are followed annually with neurodevelopmental assessments (Alberta Infant Motor Scale and Bayley Scales of Development–3), physician-validated medical and family history, and parent-reported outcomes. Potential predictors from >50 variables in demographic information; family, medical and therapy history; hormone levels; and 12 month milestones were narrowed down using backward variable selection to optimize model AIC. Linear and logistic regression was used to predict continuous and categorical variables, respectively.

Results: Of 353 participants currently enrolled, 200 (137 XXY; 22 XYY; 41 XXX) who completed 36-month visits were analysed. There were no differences in 36-month outcomes between SCT subgroups, therefore all were pooled for analyses. Higher SES and non-Hispanic ethnicity predicted higher scores for language outcomes ($p<0.05$ for all). Prenatal exposures predicted lower language and motor scores ($p=0.016$). Special education in a first degree relative ($p=0.014$) was associated with language delays ($p<0.005$). Notable variables not associated with outcomes include SCT karyotype, race, maternal prenatal health, and neonatal exam findings. Analyses of hormone levels, birth order, and proactive early therapies will be presented.

Conclusion: Results validate that well-recognized risk factors for developmental delays are also pertinent for children with SCT, including lower SES, prenatal exposures, family history of learning problems, and prematurity. Continuing to evaluate these and other early-life predictors as the cohort advances into school age will inform counseling, early developmental care, and research of targeted therapies in at-risk groups.

Keywords: XXY, Klinefelter, XYY, Trisomy X, developmental outcomes

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Abstracts for Poster Presentation

(in alphabetical order)

POSTER 1: Experiences and Concerns of Parents of Children with a 16p11.2 Deletion or Duplication Diagnosis: A Reflexive Thematic Analysis

Presenting Author: Jessica Hall

*Butter C.E.[1], Goldie C.L.[1], **Hall J.H.[2]**, Leadbitter K.[1], Burkitt Wright E.M.M.[3], van den Bree M.B.M.[2], Green J.M.[1]*

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Background: 16p11.2 proximal deletion and duplication syndromes have highly varied phenotypes, with a known propensity for lifelong psychiatric problems. This study qualitatively explored the challenges that are faced by families with 16p11.2 deletion and duplication. Our research questions were: (1) What are parents' perceptions of the ongoing support needs of families with children who have 16p11.2 living in the UK? ; (2) What are their experiences in trying to access support?; (3) In these regards, do the experiences of parents of children with duplication converge or vary from those of parents of children with 16p11.2 deletion?

Methods: We carried out structured interviews with 33 parents of children with 16p11.2 deletion or duplication. We transcribed their answers to the ADI-R question 'what are your current concerns', and we analysed these transcripts using Braun and Clarke's six step reflexive thematic analysis framework.

Results: Three themes were identified: 1) Child is Behind Peers (subthemes: developmentally; academically; socially; emotionally); 2) Metabolism and Eating Patterns and; 3) Support (subthemes: insufficient support available; parent has to fight to access support; COVID-19 was a barrier to accessing support; 16p11.2 diagnosis can be a barrier to support, child is well-supported)

Conclusion: In conclusion, parents of children with either 16p11.2 deletion or duplication shared similar experiences. However, metabolism concerns were specific to parents of children with 16p11.2 deletion. The theme Child is Behind Peers echoed concerns raised in previous Neurodevelopmental Copy Number Variant research. However, there were some key subthemes relating to research question (2) which were specific to this study. This included parents' descriptions of diagnostic overshadowing and the impact of a lack of eponymous name and scant awareness of 16p11.2.

This research highlighted how genetic disorders could act as a barrier to support, demonstrating the importance of early identification of other neurodevelopmental conditions for children with rare genetic conditions.

Keywords: 16p11.2 deletion, 16p11.2 duplication, Support, Qualitative, Children, Families

POSTER 2: The Establishment and Evaluation of the Sydney Children's Hospital Mental Health in Intellectual Disability Hub (SCHN MHID Hub)

Presenting Author: David Dossetor

***Dossetor D.R.*[1,2]**

[1] *Department of Psychological Medicine, Sydney Children's Hospital Network, Westmead, Australia*

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Background: Hypothesis: A 2 day a week multidisciplinary specialist mental health team can enhance the mental health of children and adolescents with intellectual disability and/or autism throughout NSW. Aim: To establish and evaluate a small multidisciplinary MH team to enhance MHID services through providing 1. short term assessment and treatment; 2. initiatives that enhance the capacity of mainstream services.
Methods: In 2020, NSW Health enabled funding of a multidisciplinary team for 2 days a week. Independent evaluation was conducted by UNSW Social Policy Research Centre (SPRC) led by Professor K Fisher of both the child and adult MHID Hubs, from 2021 to 2023, with mixed quantitative and qualitative methodology, including quantitative data from 386 hub participants and 142 interviews of stakeholders (hub staff, referrers, participants and their carers). Statewide service databases were accessed to assess impact on Emergency Department attendances.
Results: The services provided included: 1. free to access online webinars and the educational Journal for the Mental Health of Children and Adolescents with Intellectual and Developmental Disabilities; 2. scholarships in Stepping Stones Parent Training and Westmead Feelings Program: emotional learning for autism; discipline specific case discussions; 3. support through triage; 4. comprehensive assessment and treatment through face to face or video conference consultations, often with online multidisciplinary, multiagency video-conferences; 5. Supporting innovative approaches to treatment eg specialty Circle of Security parent groups, Parent Child Interaction Therapy; 6. Support to access appropriate disability funding.

The SPRC reported: 1. Improved access to mental health services; 2. improved wellbeing of participants, families and carers who felt more understood, involved and consulted than prior to the hubs. Holistic assessments were valued, along with support for clinicians, training, supervision, partnerships, promotion and research. 3. Telehealth was widely accepted- Sydney not a barrier to service. Over time hubs became better known with improved equity of access. 4. Advice about changing medications and behaviour management interventions was useful. 5. The flexibility of online format of webinars was valued. 6. The training was useful and relevant. 7. Mainstream staff reported increased confidence in managing patients with MHID. 8. Examination of state-wide health database found a 25% reduction in Emergency Department presentations of those seen. Success was limited by limited resources, eg for research and lived experience co-design and funding to enable longer term support. Free to access educational materials are available at http://www.schoolink.chw.edu.au.
Conclusion: Establishment of a small statewide tertiary, second opinion service for the mental health of children and adolescents with intellectual disability and autism was a cost-effective model to enhance services and build expertise. With the rising awareness of and concern for co-morbid mental health issues in this high need population, such a model can be recommended.

Keywords: Mental Health in Intellectual Disability

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POSTER 3: The Neurodevelopmental Spectrum of Synaptic Vesicle Cycling Disorders

Presenting Author: Josefine Eck

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Background: Advances in genomic technologies have enabled identification of many new genetic causes of neurodevelopmental disorders (NDDs). Genes associated with NDDs can be grouped into networks according to their molecular and cellular functions. Synaptic vesicle cycling (SVC) is one functional gene network in which rare, high penetrance variants are known to cause a spectrum of NDDs. Understanding the mechanisms contributing to the neurodevelopmental pathogenicity and variability in individuals with SVC disorders will help to provide families with evidence-based prognostic advice and improve diagnostic yield, clinical assessments and long-term management.

Methods: We systematically describe neurodevelopmental phenotypes across 100 individuals with SVC disorders (12 different single-gene diagnoses, including SYT1, TRIO, STXBP1 and DNM1) and compare these to 79 individuals with other monogenic NDDs (15 different single-gene diagnoses). Several quantitative questionnaire measures previously validated in populations with NDDs and participants' clinical reports were obtained. We applied a data-driven dimensional clustering approach to assess associations between genetic diagnoses, neurological symptoms and behavioural variation.

Results: We observed a wide range of severity across all behavioural measures within both groups. The SVC group presented with a higher prevalence of severe intellectual disability, visual impairment, epilepsy, motor impairments and self-injury. Furthermore, a genotype-blind analysis, combining clinical and neurodevelopmental dimensions, identified four phenotypic similarity clusters. Each identified cluster has membership from both SVC and non-SVC participants with an over-representation of SVC disorders in the third cluster, being characterised by high rates of neurological problems and severe global difficulties.

Conclusion: We compared clinical and neurodevelopmental characteristics of SVC and non-SVC groups, containing diverse genetic diagnoses. Although grouping genetic NDDs by functional network will not on its own improve prognostication or management, it may identify sub-populations with shared characteristics and clinical needs. As a next step, we will explore neurodevelopmental variation within SVC disorders.

Keywords: Neurodevelopmental Disorders, Synaptic Vesicle Cycle, Human Genetics, Functional Network Phenotyping

POSTER 4: Gene Therapy in Fragile X Syndrome: A Caregiver Perspective

Presenting Author: Sarah Eley

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Background: Recent laboratory studies increasingly indicate the therapeutic potential for gene therapy in fragile X syndrome (FXS). At the same time, there are human studies of gene therapy beginning for other neurodevelopmental conditions, most notably Rett Syndrome. The views of relevant communities are key to understand when planning any intervention trial, but this is particularly the case for FXS, where the clinical presentation is especially varied. We therefore set out to examine the views about gene therapy of carers and family members of people with FXS.

Methods: A questionnaire was developed, consisting of 7 open-ended questions exploring individuals views on gene therapy and 5 questions relating to characteristics of the person with FXS whom they care for. The questionnaire was distributed via the Patrick Wild Centre mailing lists and relevant charitable organisations as well as posted on social media. Following a 3 month period of data collection, a thematic analysis of the responses will be conducted, in particular examining whether there are certain themes relating to age, gender or severity of symptoms.

Results: Data collection for the study is ongoing. Initial results suggest a largely positive view of gene therapy with many respondents stating they are curious, interested and would like research to occur in the field. Notably, most respondents understanding of gene therapy is reported as being basic or limited. Proven safety and a known side effect profile were noted as important for people to consider before they would put their dependant forward for a clinical trial.

Conclusion: While no formal analysis has yet taken place, early findings suggest the community is broadly in favour of gene therapy trials taking place in FXS. More information is required to confirm these results. Community education around gene therapy is likely to be particularly important before any trials take place.

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

POSTER 5: Genotype Considerations in the FASD Phenotype: Experience in a State-Wide Diagnostic Service in Australia

Presenting Author: Elizabeth Elliott

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Background: Prenatal alcohol exposure (PAE) can result in Fetal Alcohol Spectrum Disorder (FASD), a permanent, heterogeneous condition characterised by severe neurodevelopmental impairments with or without microcephaly, characteristic facial dysmorphology and congenital anomalies. Clinical and pre-clinical studies suggest that genetic factors, in the mother or fetus, influence the phenotypic outcomes following PAE. The objectives of this study were to evaluate the prevalence and types of DNA copy number variation (CNV) in children (0-18 years) diagnosed with FASD and to identify genes known to be associated with neurodevelopmental disorders.

Methods: Chromosomal microarray (CMA) and Testing for Fragile X was performed in all children diagnosed with FASD in the NSW CICADA FASD Service - a state-wide multidisciplinary diagnostic clinic in Australia. We performed a retrospective chart review of 175 patients diagnosed with FASD between 2016-2022 to obtain data on medical and family history, phenotype, and genotype (CMA). All CMA results were reviewed by a clinical geneticist.

Results: A rare CNV was identified in 38 of 157 (24.2%) patients who had CMA testing and 40 unique CNVs were identified. In 4 patients a neurodevelopmental susceptibility syndrome was identified including Xq28 microduplication syndrome; 16p12.2 microdeletion syndrome; 17q11.2 microduplication syndrome and an atypical variant of 12q.11 deletion velocardiofacial syndrome. Two children had incidental pathogenic variants. In 32 of 38 (84.2%) cases with a rare CNV, 34 variants of unknown significance (VOUS) were identified, of which 13 encoded genes associated with common neurodevelopmental disorders. Three of 13 VOUS encoded different subunits of the voltage-dependent calcium channel complex protein (CACNB2, CACNA1A, CACNA2D3).

Conclusion: These novel results suggest that 1 in 4 children diagnosed with FASD may harbour a rare CNV of which 84.2% are of uncertain clinical significance. Genetic testing can support the FASD diagnostic process and may reveal additional diagnoses or sources of genetic vulnerability to FASD.

Keywords: Fetal Alcohol Spectrum Disorder (FASD), Prenatal Alcohol Exposure (PAE), neurodevelopmental, Copy Number Variant (CNV), genetic disorders

POSTER 6: Impact of Cannabis on the Neurodevelopmental Phenotype in FASD: A National Study

Presenting Author: Elizabeth Elliott

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Background: Like alcohol, cannabinoids including tetrahydrocannabinol cross the placenta. Prenatal cannabis exposure has been associated with cortical maldevelopment, low birth weight, hyperactivity, sleep problems, memory, and brain development in clinical and pre-clinical models. Australian Paediatric Surveillance Unit (APSU) data show 52% of children with Fetal Alcohol Spectrum Disorder (FASD) were prenatally exposed to cannabis, but its impact in FASD is poorly described. We aimed to report the neurodevelopmental phenotype and prevalence of comorbid attention deficit hyperactivity disorder (ADHD) and sleep disorder in children with FASD, with or without prenatal cannabis exposure.

Methods: Through the APSU we collected national, monthly data from paediatricians, on children newly diagnosed with FASD (January 2015-July 2023). Children aged 7-12 years were stratified according to the presence/absence of prenatal cannabis exposure (FASD+C vs FASD-C). Proportions with severe impairment in any of 10 neurodevelopmental domains, ADHD, or sleep disorder, were compared between groups using chi-squared tests.

Results: Of 365 children with FASD, 189 [51.8%] had FASD+C and 176 [48.2%] had FASD-C. The FASD+C group had significantly higher rates than the FASD-C group of severe neurodevelopmental impairment in domains of cognition (47.5% vs 37.1%; p=0.049), affect regulation (38.8% vs 27.1%; p=0.042), and adaptative function (83.3% vs 65.0%; p<0.0001); and in sleep disorders (30.9% vs 19.4%; p=0.017). However, the FASD-C group had higher proportions with severe impairment in academic achievement (71.3% vs 60.2%: p=0.04) and memory (38.8% vs 26.6%; p=0.028).

Conclusion: In children with FASD, prenatal exposure to cannabis increases the risk of sleep disorders and severe impairment in some neurodevelopmental domains but may modify risk in other domains. Although findings are consistent with previous research on the impact of cannabis on disordered sleep and neurodevelopment, the variable effects observed on function may reflect the timing or dose of prenatal alcohol and cannabis exposure or regional brain susceptibility.

Keywords: Fetal alcohol spectrum disorders, Cannabis, Prenatal exposure delayed effects, Neurodevelopmental phenotype, Sleep disorder, Child

POSTER 7: Attention Profiles in Williams Syndrome: Gaze Shift Latency, Disengagement Challenges, and Pupil Dilation

Presenting Author: Astrid Hallman

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Background: People with Williams syndrome (WS) face challenges in diverse areas of cognitive processing, including attention. Previous studies suggest that these challenges are particularly pronounced when disengagement of attention from a previously attended stimulus is required, as compared to shifting of attention without the need to disengage. Reduced disengagement could in turn be implicated in several of the behavioural characteristics of WS, including prolonged attention to faces. Here, shifting and disengagement of visual attention were assessed in one of the largest eye-tracking studies of WS to date ($n = 45$).
Methods: We investigated gaze shift latency and the impact of auditory alerting cues (cue effect) in WS individuals (age 9-57, $n = 45$), typically developing (TD) children and adults (age 9-60, $n = 36$), and TD-infants (6-7 months, $n = 32$) using a modified gap-overlap task. Data were analysed using linear mixed effect models (LMMs).
Results: Individuals with WS exhibited slower gaze shifts than the comparison groups (condition: $F(2, 172.247) = 38.386$, $p < 0.001$; group: $F(2, 99.186) = 27.255$, $p < 0.001$). The gap effect was consistent across groups, with no group differences. Robust pupil dilation correlated with auditory cues (condition: $F(1, 104.26) = 88.693$, $p < 0.001$) in all groups. WS individuals and TD-infants struggled similarly to disengage attention from central targets. Larger pupil responses increased the odds of attention disengagement failure (OR: 1.799, CI 95% [0.684, 4.732], $p < 0.001$), albeit with high uncertainty.
Conclusion: Contrasting with previous theories of attention in WS, we found no evidence for a specific challenge in disengaging attention. Instead, people with WS were slower and less likely to shift attention than the comparison groups. All groups exhibited robust pupil dilation with auditory cues, but none showed behavioural benefits from them.

Keywords: Williams syndrome, orienting attention, pupil dilation, eye tracking

POSTER 8: Evaluation of Sleep Across Single Gene Disorders Associated with Autism and Intellectual Disability Using Simons Searchlight Data

Presenting Author: Lindsay Mizen

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Background: Sleep problems are prevalent in intellectual disability and autism with a range of consequences including communication and social interaction difficulties, anxiety and depression. We compared sleep problems across single gene conditions associated with intellectual disability and autism.

Methods: We explored data from the Simons Searchlight project, an international repository for data from individuals affected by rare genetic neurodevelopmental conditions. We chose synaptic genes as these may have overlapping neurobiology. Sleep information, measured by the Child's Sleep Habits Questionnaire (CSHQ), was available for 5 of the most prevalent conditions - SCN2A, GRIN2B, SYNGAP1, DYRK1A and STXBP1. The CSHQ has 33 questions about sleep during a typical week; higher scores indicate worse sleep. In addition to Total Score, data was grouped into subscales: Bedtime Resistance, Sleep Onset Delay, Sleep Duration, Sleep Anxiety, Night Wakings, Parasomnias, Sleep-Disordered Breathing and Daytime Sleepiness.

Results: All five conditions were associated with Total Scores above the 41-threshold deemed indicative of sleep abnormalities. There was a significant difference between them though with SYNGAP1 highest and GRIN2B lowest (DYRK1A median 45.0, IQR 12.0; GRIN2B median 43.0, IQR 11.0; SCN2A median 47.0, IQR 11.0; STXBP1 median 46.0, IQR 9.50; SYNGAP1 median 48.0, IQR 14.0; Kruskal-Wallis p=0.037). Sleep Anxiety and Daytime Sleepiness were the only subscales that were significantly different (Sleep Anxiety: DYRK1A median 5.0, IQR 2.50; GRIN2B median 5.0, IQR 3.0; SCN2A median 5.0, IQR 2.0; STXBP1 median 5.0, IQR 2.0; SYNGAP1 median 6.0, IQR 3.0; Kruskal-Wallis p=0.050, Daytime Sleepiness: DYRK1A median 13.5, IQR 3.25; GRIN2B median 12.0, IQR 4.0; SCN2A median 14.0, IQR 4.0; STXBP1 median 13.0, IQR 4.0; SYNGAP1 median 14.0, IQR 3.0; Kruskal-Wallis p=0.045).

Conclusion: Sleep problems are prevalent in these 5 synaptic genetic conditions, but there are some significant differences between them. Further work is required to explore any relationship with daytime functioning.

Keywords: Sleep, intellectual disability, autism, Simons Searchlight

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POSTER 9: Probiotic Intervention for Microbiome Modifications and Consequential Clinical Improvements in Children with Fragile X Syndrome: Presentation of Pilot Study

Presenting Author: Dragana Protic

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Background: The role of the gut microbiome in Fragile X syndrome (FXS) remains largely unexplored. The relationship between FXS in humans and gut microbiota has not yet been assessed. However, there are several preclinical research which emphasize the role of dysbiosis and/or probiotics in FXS animal models. The primary objective of this clinical trial is to evaluate efficacy of probiotic mixture which contains *Lactobacillus casei, Lactobacillus salivarius and Bifidobacterium breve*, in children with FXS aged 3-18 years.

Methods: This is open-label, single-group, trial without masking, supported by FRAXA Research Foundation. Each participant receives probiotic for 12 weeks. The study enrols 15 participants with FXS, aged 3-18 years, both sexes, during 1-year-period. Subjects attend three visits (baseline, 6-week, 3-month-visits) to the Fragile X Clinic in Belgrade/Serbia. The primary outcome measures are Vineland Adaptive Behavior Scales–Third Edition and eye tracking. Exploratory endpoint is microbiome analyses. Secondary outcome measures are: CGI-S/CGI-I scores, ABC-CFX, quality of life, sleep, EEG. Exploratory objects of this trial are analyses of microbiome composition and assessment of its alterations and modifications (by probiotic mixture) that may lead to clinical improvement and prediction which patients with FXS may be likely to benefit from probiotics treatment.

Results: Study results will be available at the conference. Based on preliminary findings, the selected probiotic shows improvement in hyperactivity and attention. Some parents have reported a decrease in sleep problems among children. Previously, this probiotic mixture improved quality of life in children (n = 150; aged 3 – 17 y.) with atopic dermatitis.

Conclusion: Currently, we can only assume that daily intervention with probiotic mixture which contains *Lactobacillus casei, Lactobacillus salivarius and Bifidobacterium breve* will lead to: (i) significant microbiome modifications and (ii) consequently to clinical improvement in children, both sexes, aged 3 to 18 years diagnosed with FXS during a 3-month treatment period.

Keywords: Fragile X syndrome, probiotics, microbiome, brain processing

POSTER 10: Electroretinogram b-wave Amplitude as a Biomarker for Sensory Processing Abnormalities in Fragile X Syndrome: Correlation with FMRP Levels and Behavioural Features

Presenting Authors: Ellery Santos & Hazel Biag

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Background: Fragile X syndrome (FXS) is a neurodevelopmental disorder caused by a CGG (>200) repeat expansion in the Fragile X Messenger Ribonucleoprotein 1 (FMR1) gene promoter, leading to transcriptional silencing and deficiency of Fragile X Messenger Ribonucleoprotein (FMRP) protein. This disrupts synaptic function and neural development. Individuals with FXS often have sensory processing abnormalities, including hypersensitivity, and sensory overload. Electroretinograms (ERG) measure retinal electrical activity in response to light and provide insights into brain function. Studies show reduced ERG b-wave amplitude in FXS males, suggesting it as a potential biomarker for sensory deficits. This paper aims to (1) determine the relationship between ERG b-wave amplitude and FMRP in FXS and (2) investigate how b-wave amplitude deficits correlate with sensory and behavioural features in FXS individuals.

Methods: FMRP levels in blood (peripheral blood mononuclear cells, PBMCs) and retinal function (assessed using the RETeval device's PhNR T3 protocol, which involves 3.4 Hz red flashes against a blue background) were evaluated in individuals with FXS. Each participant's caregiver completed the Sensory Experience Questionnaire (SEQ 3.0), the Aberrant Behaviour Checklist (ABC), and the Swanson, Nolan, and Pelham Rating Scale (SNAP-IV).

Results: Preliminary results demonstrate a statistically significant correlation between ERG b-wave amplitude and FMRP levels in the FXS cohort. While initial comparisons between b-wave amplitude and clinical/behavioural measures demonstrated non-significant correlations, this may be due to the small sample size and insufficient power to detect effects. Further analysis and full results will be presented at the conference with additional enrolled subjects.

Conclusion: The study indicates that in individuals with FXS, reduced ERG b-wave amplitude is correlated with decreased FMRP levels and may correlate with sensory behaviours (underpowered). Further analysis may demonstrate that combining ERG with psychometric/sensory assessments can aid in developing targeted therapies for abnormal sensory processing in FXS.

Keywords: FXS, FMRP protein, ERG, sensory

POSTER 11: Clinician Knowledge, Confidence, and Approaches Used in the Provision of Psychological Therapy to Autistic Individuals and Individuals with Intellectual Disability in Child and Adolescent Mental Health Services: Mental Health Provider Survey

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Background: Children and young people (CYP) with a neurodevelopmental condition such as autism or intellectual disability are 4.5 times more likely to have anxiety and depression than those without a neurodevelopmental condition, known as a co-occurring difficulty. Furthermore, out of 2,803,244 individuals with co-occurring difficulties, 27.4% are under 18 years of age, highlighting the need for effective early intervention in Child and Adolescent Mental Health Services (CAMHS). The pathways created within CAMHS for autistic CYP or CYP who have an intellectual disability and co-occurring mental health difficulty may not be accessible due to limited need-specific psychological therapies available, such as Cognitive Behavioural Therapy.
Methods: A pre-existing survey from Canada has been adapted, entitled Mental Health Provider Survey, and carried out with 100 CAMHS clinicians across England, who have experience in treatment through psychological therapies with children and young people across England, used to survey clinician confidence, knowledge, skills, and training in CAMHS for autistic children and young people and children and young people with an intellectual disability and co-occurring mental health difficulties in England while investigating issues of access.
Results: The findings underscore the importance of needs-specific triage and assessment procedures, improving clinician knowledge, and adapting psychological treatment practices.
Conclusion: It concludes with recommendations for enhancing triage and assessment procedures, improving clinician knowledge and adapting psychological treatment practices. The study serves as a valuable resource for informing commissioners and policymakers about the training needs of CAMHS clinicians and strategies for enhancing triage, treatment, and assessment processes to better serve this demographic.

Keywords: CAMHS, Intellectual disability, Autism, Mental health, Psychological therapy, Learning disability

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POSTER 12: Comparing the Social Impairment Profiles of Single Gene Conditions Using Simons Searchlight Data

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Background: Autism is characterised by differences in social interaction/communication and restricted/repetitive patterns of behaviour and interests. Genetic factors are known to play an important role in the aetiology of this condition. In this study, we compared the autism trait profiles of four single gene conditions (SYNGAP1, SCN2A, GRIN2B and STXBP1) that have previously been reported to be associated with autism.
Methods: The Social Responsiveness Scale (SRS) was completed by the parents and primary caregivers of participants enrolled in the Simons Searchlight. The sample consisted of 20 SYNGAP1, 62 SCN2A, 36 GRIN2B, and 28 STXBP1 participants aged between 4-18 years.
Results: Analysis demonstrated there were no differences between the groups for either total t-score, awareness, cognition, communication, or mannerisms. However, there was a significant difference in t-scores for social motivation, with SYNGAP1 and SCN2A scoring higher than GRIN2B and STXBP1. Cluster analysis identified two distinct subgroups, with cluster 1 having higher scores on all SRS scales while cluster 2 demonstrated a milder profile.
Conclusion: These findings highlight that despite their differing genetic bases, these syndromes display similar social impairment behavioural phenotypes. Higher levels of social motivation in SYNGAP1 and SCN2A may indicate potentially different targets for intervention.

Keywords: Autism, Intellectual disabilities, single gene conditions, Simons Searchlight

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SSBP Syndrome Sheets 2024

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

Angelman Syndrome

Alternative names

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

First description

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

Genetic aspects

Angelman syndrome is caused by a disruption of the maternally inherited proportion of chromosome 15q11.2-13 (Clayton-Smith & Laan, 2003; Knoll *et al.*, 1989) via four known genetic mechanisms (Jiang *et al.*, 1998). Approximately 70% of cases are caused by a de novo deletion (Knoll *et al.*, 1989). The deletion can be further categorised as a 'Class I' or 'Class II' depending on the amount of information missing (Sahoo *et al.*, 2006), with Class I deletions representing a larger deletion, encompassing Class II. The majority of deletions in Angelman syndrome are Class II, with an estimated prevalence of between 55 and 60% of de novo deletions (Christian *et al.*, 1995). 2-7% of cases are caused by uniparental disomy (UPD; Engel, 1993; Prasad & Wagstaff, 1997), where two copies of the paternal chromosome are inherited, 2-8% of cases are caused by a mutation in the UBE3A gene (Kishino, Lalande, & Wagstaff, 1997) and 2-5% of cases are caused by an imprinting centre defect (ICD; Bürger *et al.*, 1997). In around 40-50% of ICD cases caused by an epimutation, mosaicism is identified (Buiting, 2010; see Le Fevre *et al.*, 2017 for case reports). Between 5-20% (dependent upon sample and extent of molecular investigations) of individuals with the physical and behavioural features of Angelman syndrome show no identifiable abnormalities in the 15q 11-13 region (Clayton-Smith & Laan, 2003; Williams, Lossie, & Driscoll, 2001). Explanations for when no abnormality can be detected can be that there are currently unidentified mechanisms that affect the expression of UBE3A or there is a misdiagnosis of another syndrome that is phenotypically similar to Angelman syndrome (Bird, 2014). There are several syndromes that phenotypically overlap with Angelman syndrome which can result in misdiagnosis (for reviews of 'Angelman-like' syndromes see Tan, Bird, Thibert, & Williams, 2014; Williams, Lossie, & Driscoll, 2001). The genetic association between Angelman syndrome and Prader-Willi syndrome has evok ed interest in genomic imprinting (see Brown & Consedine, 2004; Haig & Wharton, 2003 for an excellent discussion).

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

Incidence/prevalence

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

Physical phenotype

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

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Clinical phenotype

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

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

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

Behavioural aspects

The behavioural phenotype of Angelman syndrome is characterised by heightened levels of laughing and smiling, a happy demeanour, excessive sociability, aggression, impulsivity and sleep disorders (Horsler & Oliver, 2006a). Early work suggested that frequent laughing and smiling was neurologically driven, and therefore environmental factors were not influential (Williams, Frias, & Opitz, 1982). However, careful experimental manipulation of the environment identified that both the frequency and duration of these behaviours are related to environmental context, namely adult interaction (Horsler & Oliver, 2006b; Oliver, Demetriades, & Hall, 2002). Increased prevalence of aggression, not self-injury, is reported (Arron, Oliver, Moss, Berg, & Burbidge, 2011), with typical topographies including hair pulling and skin grabbing (Summers, Allison, Lynch, & Sandier, 1995). Although it has been suggested that social motivation underpins the heightened aggression in Angelman syndrome, this is not shown consistently in the literature (Allen *et al.*, 2010; Radstaake *et al.*, 2013; Strachan *et al.*, 2009).

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

Cognitive aspects

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

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

Genotype x phenotype correlations

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

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

Life expectancy

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

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Effie Pearson, Mary Heald and Chris Oliver
(Updated May 2022)

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Autism Spectrum Disorder

Classification

Although there are some slight differences between the two main diagnostic classification systems for autism (Diagnostic and Statistical Manual [DSM]-5; American Psychiatric Association, 2013; International Classification of Disorders [ICD] 11; World Health Organisation, 2018) both require evidence (currently or by history) of difficulties in two core domains: (i) the ability to initiate and sustain reciprocal social interaction and social communication, and (ii) a range of restricted, repetitive, and infexible patterns of behaviour and interests. In addition, both classifications include hyper- or hypo reactivity to sensory input and/or unusual interests in sensory stimuli. Diagnostic ascertainment should specify if autism is accompanied by additional intellectual or language impairments; is associated with a known medical, or genetic condition or environmental factor, or is associated with another neurodevelopmental, psychiatric or behavioural disorder. To meet diagnostic criteria, symptoms must be sufficiently severe to cause impairment in personal, family, social, educational, occupational, or other important areas of functioning; DSM-5 also incorporates overall severity ratings ('requiring very substantial support"; "requiring substantial support" and "requiring support"). Symptoms must have been present in early development although they may not become apparent until social demands exceed the individual's capabilities; symptom severity may also vary according to social, educational, or other contexts. Sub-categories of autism that were previously included in DSM-IV/ICD10 (e.g. Asperger Disorder, Autistic Disorder, Pervasive Developmental Disorder NOS) are no longer specified.

Associated conditions

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

Genetics

Overall heritability estimates for autism vary somewhat but median rates are around 80%. Family genetic studies indicate significantly increased rates of autism in siblings (around 20%); the "Broader Autism Phenotype" (i.e. having problems related to social, language and/or cognitive functioning) is also estimated to occur in up to 20% of first-degree family members (Thapar & Rutter, 2021) However, there is wide genetic heterogeneity, with multiple modes of inheritance including high rates of de novo mutations and a wide range of possible rare and common copy number variations (e.g. submicroscopic chromosomal deletions or substitutions), (Arnett *et al.*, 2019). Diverse clinical phenotypes and limited sample sizes add to the challenges of identifying the specific genes involved and currently only around 10% to 15% of cases of autism appear to be associated with a known genetic mutation Moreover, as research into the genetics of autism has progressed, the shared genetic influences between autism and other conditions, especially ADHD, has become increasingly clear (Ma *et al.*, 2021).

Environmental risk factors

Recent research has highlighted the impact of gene-environment interactions and a number of potential environmental risks has been identified (Hertz-Picciotto *et al.*, 2018). These include high maternal and paternal age; maternal health factors such as obesity or drugs taken during pregnancy (e.g. thalidomide, SSRI's and Valproate); immune system abnormalities; pre or peri- natal perturbations, and pre-natal exposure to pollutants and pesticides. However, there is no evidence that MMR or other vaccines are a cause of autism.

Prevalence

Prevalence estimates of autism vary, both across and within countries. The most recent systematic review update, based on 71 studies (Zeidan *et al.*, 2021), reported ranges from 1.09/10,000 to 436.0/10,000, with a median prevalence of 100/10,000 (i.e.1%). The median percentage of autism cases with co-occurring intellectual disability was 33.0%. The median male-to-female ratio was 4.2, although other studies now suggest that the apparent gender bias may be at least partly due to the fact that formal diagnostic criteria may fail to identify some autistic girls and women (Driver & Chester, 2021).

Physical Phenotype

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

Life expectancy/natural history

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

Behavioural and cognitive characteristics

Difficulties in reciprocal social communication and the presence of ritualistic and stereotyped behaviours/interests are core characteristics of autism. The onset of spoken language is often delayed and around 30% of individuals are described as remaining "minimally verbal". Although intellectual disability was once thought to be a common feature of autism, more recent research indicates that 60%-70% of autistic people are of at least average intellectual ability (Zeidan *et al.*, 2020).

Outcomes and intervention

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

Autism is a highly heterogeneous condition and interventions must be tailored to individual and family needs. For very young children, approaches with a focus on social communication are recommended. For older children, support to enhance learning and social inclusion in school is required. Many adults need help to develop self-help and independence skills, and to maintain good mental health. The provision of programmes to ensure access to college, employment, and independent living is also crucial. There are no drugs that can be used to treat autism per se, but access to adequate medical care is needed to reduce the impact of co-occurring physical and mental health problems (Fuentes *et al.*, 2021; Lord *et al.*, 2022).

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Websites:

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

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

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

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

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Patricia Howlin, Updated March 2022

CHARGE Syndrome

First Description

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

Genetics/aetiology

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

Incidence/prevalence

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

Physical phenotype

The acronym was suggested by Pagon and colleagues (1981) based on common features: C – coloboma of the eye (missing part of iris and/or retina); H – heart defects; A – atresia of the choanae (bony or membranous blocking of nasal passage); R – restrictions of growth and/or development; G – genitourinary anomalies; E – ear anomalies and/or deafness. While all six features may appear, there is wide variation in both occurrence and severity. This has led to a more refined diagnostic system (Blake *et al.*, 1998) with four major features (coloboma, choanal atresia, cranial nerve dysfunction, characteristic CHARGE ear) and a number of minor anomalies. Diagnosis is based on 3 major or 2 major and 2 minor. Other diagnostic systems have since been proposed (e.g., Hale, 2016). Diagnosis is difficult because there is great variability in presence and severity of the features.

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

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

Behavioural and psychiatric characteristics

There is variability in the presence of behavioural difficulties. Behaviour has been described as very goal directed and persistent, socially interested but socially immature, demonstrating high rates of repetitive behaviour and sensation seeking, including problems with self-regulation and transitioning between activities. The behaviours have led to diagnoses of autism, attention deficit/hyperactivity disorder, obsessive-compulsive disorder, and tic disorder. It has been proposed that pain, sensory issues, and anxiety, which produce problems with self-regulation, are major sources of the behavior (Hartshorne, Stratton, Brown, Madavan-Brown, & 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, although Skei et al., (2023) found a strength in working memory. Due at least in part to sensory impairments, language development and communication may be severely delayed. Cognitive assessment is difficult in this population, however Skie et al. (2024) found support for latent learning capacity in CHARGE regardless of degree of deafblindness.

Useful websites/associations for more information

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

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Timothy S. Hartshorne, June 2024

Coffin-Lowry Syndrome

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

Genetics and molecular biology

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

Incidence / Prevalence

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

Physical features and natural history

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

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

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

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

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

Behavioural characteristics

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

Cognitive function of female carriers may be variably affected: it can range from normal intelligence to moderate mental retardation. Frequently, they are reported to have learning difficulties at school. Obesity , depression, psychotic behavior including schizophrenia) have been described in a few female carriers. Epilepsy may occasionally develop. Stimulus-induced Drop Episodes (SIDE) may occur in response to unexpected auditory 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
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Reviewed Stewart Einfeld, June 2023

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Coffin Siris Syndrome

First description and alternative names

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

Genetics and molecular biology

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

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

Incidence/prevalence

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

Physical features and natural history

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

Behavioral and psychiatric characteristics

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

Neuropsychological characteristics

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

Available guidelines for behavioral assessment/ treatment/management

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

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

Useful Websites

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

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

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

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

Behavioural characteristics

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

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

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

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

In addition to social anxiety, other types of anxiety have been reported in individuals with CdLS including demand related anxiety, separation anxiety, generalised anxiety and specific phobias (Crawford, Waite & Oliver, 2017; Groves et al., 2022; Johnson, 2015). Low mood has also been reported in individuals with CdLS with specific diffiuclties for low interest and pleasure described (Groves et al., 2019); Nelson et al., 2014; Moss et al., 2017). These difficulties may become more prominent with age, adolescence and early adulthood may be a period of increased difficulty (Goodban, 1993; Groves et al., 2019; Groves et al., 2021; Nelson et al., 2014; Moss et al., 2017; Richards et al., 2009)

Neuropsychological characteristics

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

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

Age related change

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

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Useful websites/associations for more information

- CdLS Foundation UK and Ireland: www.cdls.org.uk
- CdLS World: www.cdlsworld.org
- FIND resources: www.findresources.co.uk
- Oliver C., Moss J., Petty J., Arron K., Sloneem J. & Hall S. (2003). *Self-injurious Behaviour in Cornelia de Lange Syndrome: A Guide for Parents and Carers*. Trident Communications Ltd.: Coventry. – Available from the CdLS Foundation UK and Ireland.
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Cri du Chat Syndrome

First description and alternative names

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

Incidence/prevalence

The prevalence of CdCS has been estimated at 1 in 50,000 live births and although the exact gender ratio is unknown, the syndrome is thought to be approximately twice as prevalent in females as in males (Niebuhr, 1978; Van Buggenhout *et al.*, 2000; Dykens *et al.* 2000).

Genetics and Molecular Biology

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

(Overhauser *et al.*, 1994). This distinctive cry is considered the most prominent clinical diagnostic feature of the syndrome (Mainardi *et al.* 2006). Though relatively rare, CdCS represents the most common deletion syndrome in humans (Cornish *et al.* 2001)

Physical features and natural history

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

Behavioural characteristics

Sleep difficulties are a significant problem in this group, occurring in between 30 to 50% of individuals (Maas *et al.*, 2009). Repetitive behaviours are generally less common in CdCS than inother genetic syndromes. However, Moss *et al.* (2009) report that an attachment to specific objects is a marked characteristic of the syndrome. Occurring at a clinically significant level in over 67% of individuals, the frequency of this behaviour is significantly higher in CdCS than in other genetic syndromes including and in comparison to individuals with intellectual disability of heterogeneous cause. This behaviour differs from

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that commonly seen in autism spectrum disorder as it is typically focussed on one specific item (as opposed to a class of items) and the item may change over time. Additionally, the behaviour tends to become less marked with age.

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

Hyperactivity is a commonly reported feature of CdCS. Findings vary from reports of no increase in level of activity (Baird *et al.* 2001) to 90% prevalence rates of hyperactivity (Cornish *et al.*1998) with clinical hyperactivity (ADHD) reported to be more prevalent in CdCS than in an intellectual disability comparison group (Cornish & Bramble, 2002). The available literature documents the contrast between high prevalence of Attention Deficit Hyperactivity Disorder (ADHD) and the commonly identified immobility and severe motor delay (Cornish & Bramble, 2002). The reported high prevalence of ADHD like phenomena has raised concerns regarding both the restrictions this may place on cognitive and emotional development (Cornish *et al.*, 1998) and its role in determining familial stress (Cornish & Bramble, 2002). This highlights a need to clarify prevalence as recommendations are often made for a relatively low threshold for medication in treating hyperactivity in these individuals (Dykens & Clarke, 1997) even though there is some evidence identifying intensive behaviour modification as the most effective intervention (Wilkins *et al.*, 1983).

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

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

Neuropsychological characteristics

Early reports on CdCS suggested that profound intellectual disability was a common feature of the syndrome (Niebuhr, 1978). More recent, albeit limited, research data indicate that there is a wider range of cognitive ability (Cornish, 1996; Cornish *et al.* 1999). Progression in motor development is delayed and adaptive behaviour within the domains of socialisation, communication, daily living skills and motor skills does not appear to show any significant strengths or weakness, although no contrast groups have been employed in research studies (Cornish *et al.* 1998). Marinescu *et al.* (1999) found no association between the size of the genetic deletion on 5p and scores on the Vineland Adaptive Behavior Scales. However, individuals with translocations have been found to have a more severe developmental delay, heightened social withdrawal and more autistic-like features than those with deletions (Dykens & Clarke, 1997; Mainardi *et al.* 2006; Sarimski, 2003).

Useful websites/associations/resources for more information

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

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

Epidemiology

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

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

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

Genetics

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

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

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

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

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

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

2015). Rare individuals with Down syndrome who have incomplete trisomy and only two copies of *APP* (disomy) do not appear to have the same AD risk (Doran et al., 2017). Triplication of *APP* leads to increased deposition and accumulation of amyloid-beta protein throughout life. Duplication of the *APP* gene in the absence of Down syndrome is known to be sufficient to cause early onset AD (Sleegers et al., 2006).

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

Phenotype

Trisomy 21 is associated with a number of common characteristics but there is considerable individual variation. Intellectual disability is present to some degree in all patients with full trisomy 21 but varies from mild disability to severe and profound. Motor dysfunction occurs frequently and individuals with Down syndrome can exhibit clumsy sequences of movements, with poor control of motor sequences, timing and force. Motor dysfunction in people with Down syndrome is accompanied by hyporeflexia and reduced muscular strength and tone (Antonarakis et al, 2020). Most adults with Down syndrome are of short stature (70%), with a characteristic facial appearance. Their eyes slope upwards and outwards as a result of alterations in the structure of the surrounding tissues ("upslanting palpebral fissures"). The nose has a wide bridge, and the head an unusual shape ("brachycephaly"). Protruding tongue is present in 45% of children with Down syndrome. Limb abnormalities include a single transverse crease on the palm (85%), a large cleft between the first and second toes, and relatively short upper arms.

Physical Health

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

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

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

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

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

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

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

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

Mental Health

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

An increasingly recognised condition is Down syndrome regression disorder. Adolescents and young adults present with loss of skills and independence compared to their previous levels of functioning. There is often withdrawl from activites and up to 90% of people show language regression. Features can appear similar to catatonia including stereotypes, reduced voilition and psychomotor slowing. It is estimated that around 50% of people make a partial or full recovery, with 35% stabilising at a poorer functioning level (Santoro et al, 2020). At present the cause of this decline is unknown, although it has been suggested that the decline can occur after exposure to emotional stressors (Mircher et al., 2017). An inflammatory or autoimmune aetiology has been suggested. There is often a poor response to anti-depressant and antipsychotic medication. Electro-convulsive therapy, steroids and intravenous immunoglobulins have been trialled with some sucess in subgroups of individuals, but many individuals do not fully recover.

Behavioural characteristics

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

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

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

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

Cognitive characteristics

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

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

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

Alzheimer's disease and dementia

In adults with Down syndrome, brain changes typical of Alzheimer's disease (AD) usually develop by the fourth decade of life, and dementia is now considered to be the leading underlying cause of death in older adults with Down syndrome (Hithersay et al., 2018). Intra-neuronal amyloid-beta deposition starts as early as the first decade, with extra- cellular diffuse plaques observed in adolescents with Down syndrome (Fortea et al 2021). On post-mortem examination, almost all adults with Down syndrome over the age of 35 have the brain changes characteristic of Alzheimer's disease (i.e. amyloid plaques and neurofibrillary tangles) (Mann & Esiri, 1989; Wisniewski, Wisniewski, & Wen, 1985).

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

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

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

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

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

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

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Annapia Verri, September 2014
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Fetal Alcohol Syndrome/ Alcohol Related Neurodevelopmental Disorder/ Fetal Alcohol Spectrum Disorders

First description and alternative names

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

Genetics and molecular biology

Both FAS and ARND are teratogenic conditions, but recent research is beginning to study the epigenetic effects of prenatal alcohol exposure. For example, the major liver pathway of oxidative metabolism which produces acetaldehyde by cytotoxic alcohol dehydrogenase is also accompanied by a reduction in NAD to NADH. There is a subsequent alteration in the cellular redox triggered by a change in the NAD/NADH ratio which may result in gene activation resulting in a change in gene expression. Increasingly the impact of prenatal alcohol on epigenetic mechanisms has also been investigated. For example, studies have demonstrated that prenatal alcohol exposure has the ability to modify methylation of the retrotransposon prior to the AVY gene in genetically inbred mice, leading to differences in coat colors (17). A wide range of mechanisms beyond this have been identified, from direct apoptotic damage, interneuronal signaling deficits and damage to scaffolding proteins interfering with neural migration (18). The interface between direct and indirect effects lead to a complex presentation with over 428 different presentations and comorbidities being found to be linked to FASD (37,38)

Incidence/ prevalence

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

Physical features and psychiatric characteristics

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

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

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

Neuropsychological Deficits

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

Brain structural abnormalities

Autopsy reports of infant deaths and MRI studies showed diffuse structural brain changes. These include hydrocephalus, microcephaly, corpus callosal agenesis, cerebellar hypoplasia, enlarged ventricles and 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

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

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

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

Useful websites /associations for more information

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

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Fragile X Syndrome and Fragile X-associated Disorders

First described

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

Genetic aspects

There is sex-linked transmission because the *FMR1* gene is on the bottom end of the X chromosome (Xq27.3), so males are affected more severely than females. There is an expansion of the CGG repeat in the promotor region of the *FMR1* gene through the generations but progression to a full mutation (>200 CGG repeats) only occurs when it passes through a woman to the next generation. Ninety percent of males with a full mutation (>200 CGG repeats) have intellectual disability and the rest have learning and/or emotional problems. When the CGG repeat in the promotor region of *FMR1* is greater than 200 there is typically methylation of the FMR1 gene. However, those males with fragile X syndrome who are high functioning (IQ>70) are mosaic (some cells with the premutation (55 to 200 repeats) or partially/completely unmethylated so that some FMRP is produced. In females with fragile X syndrome there is one X chromosome that is normal and the second X chromosome with the full mutation. In these females approximately 25% have intellectual disability and an additional 60% have learning difficulties particularly in math, attention and impulsivity. Some females with the full mutation have no intellectual disability and very few clinical problems and these individuals usually have a favorable activation ratio, meaning the majority of their cells have the normal X as the active X as measured in blood. The diagnosis of fragile X syndrome is made by *FMR1* DNA testing. Cytogenetic studies may also show the fragile site in folate deficient media, but DNA studies are essential for diagnosis and to identify the CGG repeat expansion number. More recent whole genome and whole exome studies have documented point mutations and deletions in *FMR1* that can lead to a fragile X syndrome phenotype without the CGG expansion because the FMRP is abnormal or partially deleted.

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

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

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

Incidence/Prevalence

The allele frequency of the full mutation is 1 in 4000 to 6000 in the general population, however some individuals with the full mutation especially females do not have intellectual disability, although their learning difficulties and emotional problems still constitute fragile X syndrome. The premutation is more common and 1 in 130-250 females and 1 in 250-800 males in the general population have the premutation. Some parts of the world including Colombia, Israel and Mallorca have a much higher prevalence of the premutation and the full mutation likely related to founder effects.

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

Physical Features in Fragile X Syndrome

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

Life expectancy/Natural history

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

Behavioural characteristics

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

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

Social impairments, ASD, ADHD and social anxiety with aversion to eye contact are present in the majority of children and adults with fragile X syndrome. Approximately 60% of men will have an autism spectrum disorder (ASD). The rest are socially responsive and affectionate individuals with good understanding of emotions, although autistic like features such as perseverations, hand flapping and poor eye contact with shyness are seen in the majority. Self-injury, notably hand biting and aggression provoked by frustration, anxiety and excitement are common. Hand flapping is seen in the majority both with and without autism. Obsessive and compulsive features are common and often lead to rituals and picky eating habits. Mouth stuffing, tactile defensiveness and overreaction to sensory stimuli leading to hyperarousal and tantrum behavior are seen in the majority. Approximately 30% of males have aggression; and anxiety associated with hyperarousal is a component of this aggression. Individuals with fragile X syndrome have a GABA (inhibitory) deficit and this leads to a lack of habituation to sensory stimuli both in electrodermal studies and also in fMRI studies. The lack of habituation to sensory stimuli in the CNS is correlated to the severity of ASD in females. Hyperactivity is seen in about 80% of boys although attention problems and impulsivity without hyperactivity can be seen in 40% of girls with the full mutation.

Treatment

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

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

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

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

Resources

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

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Klinefelter Syndrome (47,XXY)

First description and alternative names

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

Genetics and molecular biology

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

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

Incidence/prevalence

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

However, prenatal 47,XXY diagnoses may be increasing through advances in prenatal screening such as non-invasive prenatal screening (NIPS) with confirmatory prenatal (amniocentesis or chorionic villus sampling) or postnatal (chromosomal microarray or chromosome karyotype) testing. A chromosomal microarray (CMA) test consists of a blood sample or oral cheek (buccal) swab. Cheek swabs are an easy and painless way to detect abnormalities of chromosome numbers to provide a definitive diagnosis.

Physical features and natural history

Although 47,XXY is associated with a characteristic pattern of physical differences, the degree to which an individual is affected varies widely. Males with 47,XXY have been traditionally described as tall, with narrow shoulders, broad hips, sparse body hair, gynecomastia, small testes, and androgen deficiency. Post-pubertal males may manifest infertility, gynecomastia, lack of complete pubertal virilization, testicular failure, azoospermia and elevated gonadotropin levels, with decreased 17-ketosteroid levels. Studies investigating the efficacy of targeted administration of male hormones (androgens), such as testosterone enanthate, in boys with 47,XXY have shown to alleviate feminization effects that may have occurred due to insufficient testosterone levels, while also promoting the development of secondary male sexual characteristics. Other areas of increased risk developing over adulthood include low energy and libido, osteoporosis, thromboembolic disease, obesity, and diabetes mellitus. Recently, studies have demonstrated the positive effect of testosterone treatment on the well-being and neurocognitive profiles of boys with 47,XXY (Samango-Sprouse *et al.*, 2013; 2018). Testosterone treatment in boys with 47,XXY have also been shown to decrease anxiety and increase motor proficiency (Samango-Sprouse *et al.* 2013; 2015). Individuals with a mosaic form are often less affected and may have normal fertility.

Behavioral and psychiatric characteristics

Individuals with 47,XXY are at increased risk for behavioral problems and psychiatric disorders. Behavioral problems are variable in incidence—although the child with a prenatal diagnosis presents with fewer problems (Ross *et al.*, 2012; Samango-Sprouse *et al.*, 2013; 2015). Additionally, boys receiving early hormonal treatment in infancy or early childhood have fewer problems than the untreated child or the child postnatally diagnosed (Samango-Sprouse *et al.*, 2015, 2021). School-aged children frequently show problems with anxiety and mood dysregulation, self-esteem, and socialization. Socialization problems

frequently relate to inhibition and anxiety, and they may become more pronounced during adolescence especially without hormonal treatment. Some of these problems may originate from frustration stemming from a relatively low expressive ability as compared to receptive skills (Simpson *et al.*, 2003; van Rijn *et al.*, 2006). Testosterone replacement therapy may minimize these neurodevelopmental dysfunctions, specifically early hormonal treatment (Ross *et al.*, 2014; Samango-Sprouse *et al.*, 2011, 2013, 2015, 2018, 2021).

Neuropsychological characteristics

Emerging neuroimaging technology has increased and improved our understanding of the relationship among brain development, neurocognition, and behavioral outcome—especially in boys with 47,XXY (Giedd *et al.*, 2007). Studies on boys with 47,XXY utilizing these neuroimaging techniques have revealed reduced total brain volumes that are specifically seen in the frontal, caudate, and temporal (especially left) regions of the brain (Giedd *et al.*, 2007). Abnormalities in frontal and caudate brain MRIs are similar to those seen in MRIs of boys with ADHD, and indicative of the executive dysfunction seen in boys with 47,XXY (Giedd *et al.*, 2007; van Rijn and Swaab, 2015). The temporal lobes are associated with language capacities involving reading, social language, and processing of spoken information—all of which are notably challenged in untreated males with 47,XXY (Shen *et al.*, 2004; Savic, 2012). Abnormalities in the caudate nucleus are believed to adversely affect speech and language, as well as to manifest as the dyspraxia and oral motor dysfunction that is often found in 47,XXY boys (Giedd *et al.*, 2007). The gray matter density in the insula region of the brain in these boys is also decreased, which is linked to social and emotional processing issues (Nagai *et al.*, 2007). The parietal lobe, however, is relatively unaffected when measured by cortical thickness and volume (Giedd *et al.*, 2007). The preservation of this region is evident in the enhanced spatial cognitive skills in males with 47,XXY (Samango-Sprouse and Law, 2001; Savic, 2012). Many 47,XXY males have normal or above average cognitive capacity with typically higher nonverbal IQs and lower Verbal IQs .

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

Available guidelines for behavioral assessments/ treatment/management

Once the individual or fetus is diagnosed with 47,XXY, it is important to seek consultation with medical professionals and health care professionals who are familiar with 47,XXY for recommendations regarding resources, appropriate biological and neurodevelopmental therapies, as well as medications for ADHD or anxiety (Samango-Sprouse & Gropman, 2016). Early interventional therapies (e.g., physical, occupational, and speech therapies) are recommended throughout early childhood when discrepancies or deficits are identified to enhance early neurodevelopmental outcomes. Physical therapy is indicated when there is hypotonia, motor delay, and/ or poor coordination and is most effective between 4 and 18 months in order to develop independent ambulation skills. Occupational therapy should be considered for the boys with decreased muscle tone in the trunk or upper body, because these deficits will affect handwriting, posture, attention, and eventual school success. This type of evaluation may be most beneficial between 4 and 6 years of age and typically is needed for 12 months. Specific speech and language therapies should address speech delays with motor planning deficits, language formulation abnormalities and syntactical delays. Speech therapy should focus on eliminating oral motor weakness and dysfunction through a sensorimotor approach. Because of

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decreased muscle tonus and androgen deficiency, an active health style is encouraged from infancy through adulthood.

Androgen replacement therapy can improve bone density, increase muscle mass and strength, produce more masculine body contour, and decrease body fat. Infants with 47,XXY experience the neurotypical "mini-puberty" in which testosterone levels surge, though at a significantly reduced rate (Forest *et al.*, 1974, Lahlou *et al.*, 2004). Early hormonal treatment (EHT) may mitigate these testosterone levels and keep these infants on an appropriate neurodevelopmental track (Davis *et al.*, 2019, Samango-Sprouse *et al.*, 2020, 2021). Testosterone can produce adequate pubertal maturation with increased body hair, penile enlargement, and male distribution facial and body hair.

Useful websites/associations for more information

- The Association for X and Y Chromosome Variations (AXYS) https://genetic.org/variations/about-47xxy/
- The Focus Foundation http://thefocusfoundation.org/x-y-chromosomal-variations/xxy/
- Genetics Home Reference https://ghr.nlm.nih.gov/condition/klinefelter-syndrome
- Genetic and Rare Diseases (GARD) Information Center https://rarediseases.info.nih.gov/diseases/11920/47-xxy
- Klinefelter's Syndrome Association UK http://www.ksa-uk.co.uk/
- National Organization for Rare Disorders https://rarediseases.org/rare-diseases/klinefelter-syndrome/

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Lesch-Nyhan Disease (LND)

First Description & History

Historically, Lesch-Nyhan syndrome is the designated term for this disease; however, Lesch-Nyhan Disease (LND) and hypoxanthine-guanine phosphoribosyl transferase (HPRT, HGprt) deficiency are also used to describe this disease.

It is interesting that the first description of Lesch-Nyhan Disease may have been in the year 1267. Beck in 1991, identified an original description of what may be LND when he uncovered several cases of self-injury, gout, and intellectual disabilities in individuals living in a small village in England where St. Thomas, Archbishop of Canterbury, had been killed. The original account, written by Jacobus de Voragine, suggested that the disease might somehow be related to the murder of St. Thomas and the "wrath of God". We have come slightly further in our understanding of the disorder since then and since the first description of the familial nature of the disease (Nyhan et al. 1964, 1965).

Nyhan was the first to describe the familial nature of the disease. His work demonstrated that mutations in the hypoxanthine guanine phosphoribosyl transferase (HPRT) gene, leads to the lack of its enzymatic activity. Dysfunction of HPRT, disrupts the purine metabolism, adversely influencing neurodevelopment and leading to the neurobehavioral phenotypes (Nyhan, 1997) and to an excess of uric acid with many systemic consequences including hyperuricemia, formation of bladder calculi, and painful gouty arthritis. (Torres et al.2007). However, HPRT deficiency results in a broad spectrum of clinical involvement, which depends on the severity of the enzyme deficiency, where an activity of less than 1.5%, is at the severe end of the spectrum. Two less severe variants include HPRT related hyperuricemia, known as Keeley–Seegmiller syndrome which present with an enzymatic activity varying from 8% to 60%, and hyperuricemia with neurological disability, characterized by an enzymatic activity of 1.5-2% with hyperuricemia and neurological symptoms (Nanagiri and Shabbiri 2022).Measurements of blood HPRT activity is still, to date, the gold standard for diagnosing LNS (Nyhan, 2005).

In 1959, two physicians, Catel and Schmidt, described what has turned out to be the first variant of the disorder of partial HPRT deficiency (Kelley-Seegmiller syndrome) which, in turn, involves a variable degree of neurological symptoms without the self-injurious behavior of LND. Two variants of classic LND have been further characterized by Dr. Jinnah and colleagues (2010). These individuals have higher levels of enzyme activity than patients with the classic form and do not have the feature of self-injurious behavior. Elevated levels of uric acid are commonly present in all three types of LND. Seegmiller discovered the enzyme defect in the purine salvage pathway in 1967. Of interest, in 1960, Riley described gout and cerebral palsy in a 3-years old that may be the first classic case of LND in the literature. Hoefnagel et al, in 1965, were the first to suggest it was X-linked. In 1983, Wilson and Kelly identified the first specific mutation at the molecular level: a single nucleotide change in the codon for aspartic acid 193 -- GAC for AAC. This discovery has turned out to be one of many, many different nucleotide changes identified in this gene!

Incidence and Epidemiology

LND is a rare inborn error of metabolism disorder that affects mainly males with an estimated incidence between 1:235,000 and 1:380,000 live births in the US (Torres et al. 2007). Studies show that it occurs in relatively equal frequencies in all populations. Because it is an X-linked recessive mutation, it ought to occur only in males, but there have been several documented cases in females – although the lower severity and penetrance can be likely explained by the Lyon hypothesis, so that males who receive from the carrier mothers, the X chromosome carrying the mutated gene, will express the disease while females are mostly carriers but can develop the disease if X chromosome carrying the defective gene is expressed phenotypically.

Genetic aspects

LND is a rare X-linked, recessive genetic disorder caused by a deficiency of hypoxanthine-guanine phosphoribosyltransferase (HPRT) enzyme, located at a q26-27 position on the long arm of the X chromosome (Figure 1).

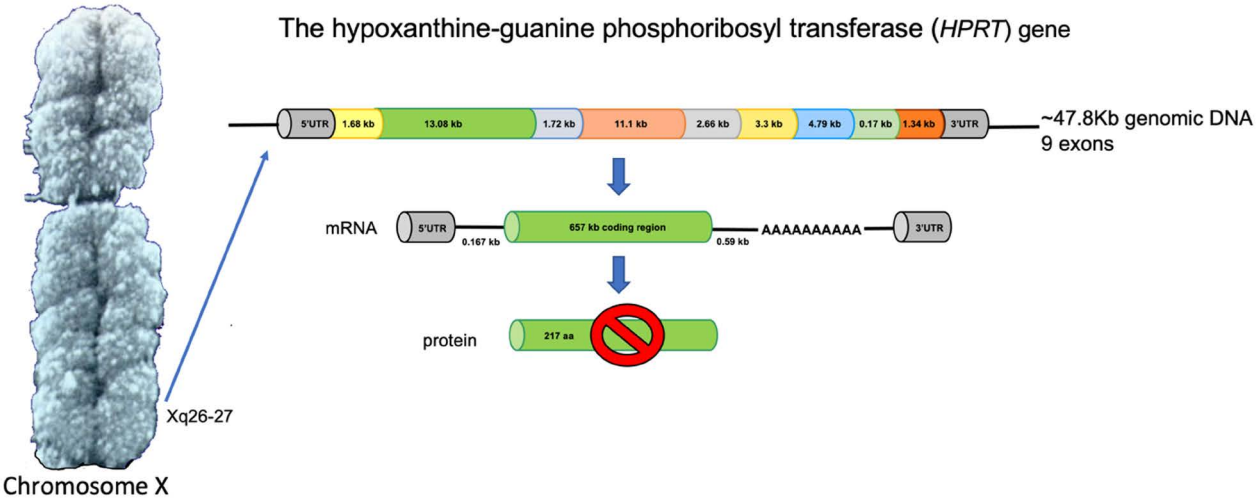

Figure 1. The HPRT gene is located on chromosome X q26-27. It spans approximately 48Kb of genomic DNA and contains 9 exons. The gene encodes for a 217 amino acid protein, which lack of function leads to functional significant purine overproduction and ultimately to neural problems.

The enzyme is a transferase that catalyzes the conversion of hypoxanthine into inosine monophosphate and of guanine to guanosine monophosphate. This enzyme plays a central role in the generation of purine nucleotides through the purine salvage pathway (Figure 2).

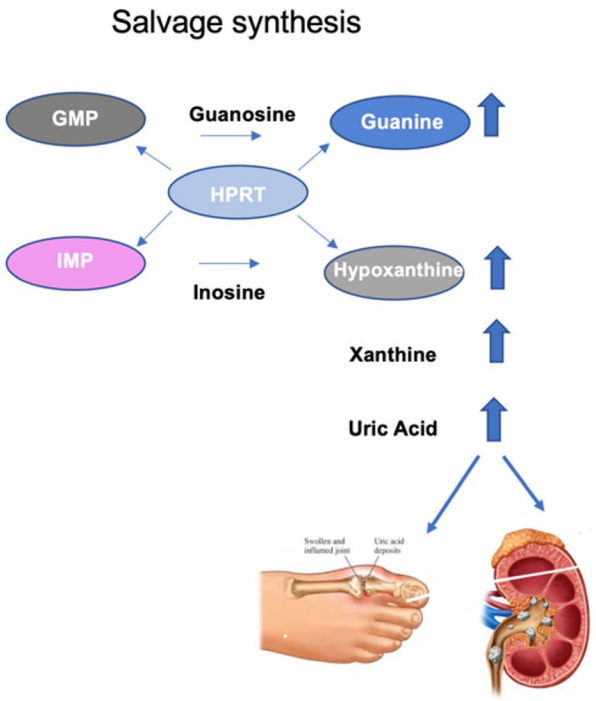

Figure 2. Deficiency of salvage nucleotide synthesis. LND is caused by the deficiency of the purine salvage enzyme HPRT which is responsible for the conversion of hypoxanthine into inosine monophosphate (IMP) and of guanosine into guanosine monophosphate (GMP). After their synthesis they are converted to nucleotides that are used for DNA repair and synthesis. The lack of HPRT also leads to increased uric acid, which accumulation leads to gout and kidney stones.

Lack of the enzyme causes an increase in guanine and hypoxanthine, which eventually gets converted into uric acid. There are probably a few thousand individuals with this disease in the world. The mutations are within the HPRT1 gene located on the long arm of the X chromosome. Remarkably, over 600 different mutations have been identified in different families (O'Neill et al. 2004), each leading to varying levels of severity of clinical presentations making HPRT enzyme deficiency a spectrum rather than a single disease (Fu et al. 2014).

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Clinical, cognitive, and behavioral features

Individuals with LND are asymptomatic at birth with normal prenatal growth and development. Typically hyperuricemia is present at birth, and orange-colored crystals in the diapers is the only clinical evidence hyperuricemiam, which leads to crystalluria, urolithiasis, nephrolithiasis, gout, and juvenile arthritis. In addition to hyperuricemia, LND is associated with cognitive impairment, renal involvement as well as severe and involuntary self-injurious behaviors.

Although it is appropriately considered a metabolic disease involving the absence, or near absence of the enzyme HPRT, because among other deficits, patients with LND have reductions of dopamine in the basal ganglia, it is tempting to think of this disease as a basal ganglia disorder, even though other areas of the brain are involved as well. From the motor disorder standpoint, LND is best described as dystonia superimposed upon hypotonia, although chorea, spasticity and athetosis have been described. During volitional movements, the examiner may believe increased tone is present, yet when the movement is over or when the patient is relaxed, hypotonia is clear. Further, anxiety often confuses the clinical picture, as it does with other aspects of the disorder, especially when the patient is examined by a physician unfamiliar with the patient. The question of the presence of athetosis vs dystonia and the presence of hypotonia vs spasticity is often difficult to distinguish on exam by a physician who is not familiar with the behavioral manifestations of LND. LND presents in the first few months of life as a developmental delay and may be diagnosed initially as cerebral palsy. Individuals with classic LND are generally non-ambulatory.

The basal ganglia are known to be involved in the regulation of areas other than the motor circuits, including personality, cognition, and emotion (Visser et al. 2000).

Although there may be significant bias and scatter, depending on who administers the IQ testing, the range of IQ scores varies but is generally in the mild to moderate intellectual disability range although some authors feel that it is lower, ranging from 40 to 80. The LND behaviors and neurological problems limit the validity of standard IQ tests. Patients with LND can be very engaging and personable and are often able to recount scores of local sporting events on a routine basis. It is interesting that parents often believe IQ scores obtained are artificially low and reason that low performance is secondary to LND behavior.

The behavioral phenotype of LND, physical and emotional self-injury, including severe self-mutilation and aggressive behavior, are generally involuntary in nature, thus, not under the patient's control. These self-destructive behaviors, one of the hallmarks of LND, usually begin between ages three and six and often escalate as the patient ages and the patient is more physically able to cause self-injury. The first manifestations of physical self-injury are lip biting, finger biting, and biting of the oral cavity.

Modes and patterns of self-injury have been previously described in Robey et al. and are often specific to each individual patient and appear consistent over the lifespan. Patterns of association involve self-injury to or about: 1) external surfaces or 2) oral or biting, usually of the lips and fingers. If a patient tends to injury him or herself using external surfaces, this pattern tends to continue throughout the lifespan. If the self-injury involves oral cavity or biting, then this pattern will re-occur throughout the lifespan. Forms of self-injury include eye-poking, head banging, fingers in wheelchair spokes, and extension of arms in doorways. Emotional self-injury, or outwardly directed aggressive behaviors, include hitting, kicking, head-butting, biting others, spitting, swearing, ethnic slurs, inappropriate remarks to the opposite sex, frequently changing opinions, and/or lying. When oral self- injury is present, removal of the teeth is essential to prevent facial disfigurement. Decisions regarding dental extraction must be made with physicians who are expert in the comprehensive care of patients with this disorder (www.Lesch-Nyhan.org).

Treatment

Management of LND syndrome is complex, thus understanding the neurological manifestations of HPRT defect allows for a thorough understanding of the disorder and subsequent comprehensive management strategies.

Since the 1960's we have known that because of the lack of HPRT, there is an over-production of uric acid and subsequent uric acid stone formation, the

xanthine urolithiasis (xanthine stone formation is due to dose specific issues of allopurinol.) Allopurinol is a drug that blocks the conversion of hypoxanthine and xanthine to uric acid by inhibiting the xanthine oxidase enzyme, representing the cornerstone of treatment of hyperuricemia. Although Allopurinol is used to lower the elevated serum uric acid, it must be titrated to maintain serum uric acid in the critical window that attenuates the neurologic and systemic consequences of hyperuricemia while avoiding xanthine stone formation. Historically, levels of the serum uric acid have been kept in a range that minimizes the formation of uric acid stones, yet not too low as to lead to the formation of xanthine stones. Unfortunately, treatment of the elevated serum uric acid with allopurinol does not have an impact on the neurobehavioral manifestations of the disease. However, as previously mentioned, since the hyperuricemia is present early during the development, early intervention can avoid many potential complications.

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 LND 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.

Deep Brain Stimulation (DBS) has been tried worldwide in numerous patients with LND to decrease the degree of dystonia. In this procedure neurosurgeons place two stimulators in the basal ganglia, like the stimulators used in other movement disorders such as Parkinson's disease. The results suggest a decrease in dystonic movements as well as a decrease in self-injurious behavior; however, it is unclear if this will become a standard treatment option due to variable effects and complications of the surgery. Finally, the use of gabapentin and botulinum injections have been tried with somewhat a reduced self-abusive behavior (Dabrowski et al. 2005).

Life expectancy

Life expectancy is a difficult issue to address as the extent of the associated clinical conditions of LND has not yet been fully characterized. Fortunately, due to the use of allopurinol, which acts as a substrate for xanthine oxidase, patients with this disorder should no longer die of renal complications. There is a suggestion that some patients may die suddenly in their twenties and thirties possibly because of an unexplained neurological event. Certainly, as the accompanying clinical conditions are managed a longer life expectancy can be anticipated.

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Lowe Syndrome

First description and alternative names

Lowe syndrome was first described in 1952 by Dr. Charles Lowe (Lowe et al., 1952). Other names for Lowe Syndrome include cerebrooculorenal syndrome, Lowe oculocerebrorenal syndrome, oculocerebrorenal syndrome, oculocerebrorenal syndrome of Lowe, phosphatidylinositol-4,5-bisphosphate-5-phosphatase deficiency, and OCRL1 syndrome. Lowe syndrome is often referred to medically as oculocerebrorenal syndrome because of the three main organ systems involved (eyes, brain, and kidneys).

Genetics

Lowe syndrome is caused by a mutation or alteration to the OCRL gene on the X chromosome. This gene is responsible for coding an enzyme that helps to regulate the production of certain cells, of which seem to impact primarily the retina, brain, and kidneys (Bökenkamp & Ludwig, 2016; Loi, 2006). The exact mechanism that leads to these three organ systems being primarily affected is not yet known. The OCRL gene has been found to highly expressed in the human hypothalamus, pituitary and other endocrine tissues, areas known to play a role in growth regulation. It is suspected that absence of this gene contributes to the short stature seen in LS and that this may be amenable to growth hormone therapy in future treatment developments (Sena et al., 2022).

A diagnosis of Lowe syndrome is most often confirmed through an enzyme deficiency analysis, usually done by taking a small skin sample. It can also be diagnosed clinically and through DNA analysis (Lewis, 2001). Diagnosis can occur before or after birth. Female carriers of the gene causing Lowe syndrome can be tested, as they usually show changes in the lens of their eye from the age of 10, which can be identified by an ophthalmologist (Röschinger et al., 2000). Carrier status can also be identified through DNA analysis and family history.

Differential Diagnosis

Generalized congenital infections, such as Rubella, are associated with a combination of congenital neonatal-onset cataracts, hypotonia, and kidney dysfunction and should also be considered as a differential diagnosis. There are also a number of different rare genetic conditions that affect similar organ systems to Lowe syndrome, resulting in overlapping symptomology. Overlapping and distinguishing features of other genetic conditions can be found on Gene Reviews (Lewis, 2001).

Prevalence

Lowe syndrome is a rare genetic condition with an estimated prevalence of 1 in 500,000 individuals (Bökenkamp & Ludwig, 2016). It is believed to occur worldwide. Because the condition is X-linked, it primarily affects males. As females have two X chromosomes, it is extremely rare for girls to have Lowe syndrome because both copies of the X chromosome would need to be affected.

Clinical and Physical Phenotype

Vision

Cataracts are present at birth in nearly all cases of Lowe syndrome (Sena et al., 2022). In addition, infantile glaucoma occurs in approximately half of individuals with Lowe syndrome, where there is too much pressure in the eye, causing eyes to become enlarged or appear bulging (Kruger et al., 2003; Loi, 2006; McSpadden, 2000).

Kidney Function

Affected males have varying degrees of proximal renal tubular dysfunction of the renal Fanconi type. In a survey of clinical symptoms by the Lowe Syndrome society, 55.4% of individuals were reported to have kidney calcification, and 21.9% to have renal stones (Sena et al., 2022). Progressive renal tubular injury is thought to eventually lead to chronic kidney disease and end-stage renal disease for many individuals between the second and fourth decades of life.

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Facial Characteristics
Elongation of the face is sometimes a feature of Lowe syndrome. Prominent forehead, deep-set eyes, high-arched palate, and fair complexion are also common.

Oral Health
Dental problems are common in LS and are reported by approximately half of parents (Sena et al., 2022). There is often a delayed eruption of adult teeth and overcrowding in the mouth. Teeth will often have white spots due to thin enamel and excessive calcium deposits (Harrison et al., 2000). Cysts can appear in the mouth and gums, leading to infection. Despite the high prevalence of dental problems reported in LS, parents report difficulties accessing dental appointments and supporting dental hygiene at home (Lowenstein et al., 2023).

Musculoskeletal
Hypotonia is present after birth (weak muscle tone), which can cause difficulties with feeding and obtaining motor milestones. Seventy-five percent of boys with Lowe syndrome are able to walk independently between the ages of 6 to 13 years old (McSpadden, 2000). Around 28.5%-50% of individuals with Lowe syndrome develop scoliosis (McSpadden, 2000; Sena et al., 2022). Rickets is common in Lowe syndrome and can often lead to bowing of the legs; however, this can often be prevented with medical treatment. Most individuals with Lowe syndrome will usually have a short stature and fall below the 10th percentile for height (Sena et al., 2022).

Low phosphorus levels may occur in approximately 41.6% of individuals, low vitamin D in approximately 70.2%, with frequency of bone fractures reported to be common at approximately 46% of individuals (Sena et al., 2022).

Puberty
Puberty is often delayed in onset, and between 33-47% of males may experience cryptorchidism (undescended testes; Recker et al., 2014; Sena et al., 2022).

Other
Cysts can often appear in the mouth and skin, such as in the gums, buttocks, and low back, which can cause pain and are at risk of infection (Ikehara & Utani, 2016). Seizures occur in approximately 45- 50% of individuals with Lowe syndrome. There is no specific seizure type (Erdogan et al., 2007; Sena et al., 2022).

Development and Cognition
Although most people with Lowe syndrome will eventually be able to walk, difficulties with motor skills often persist, leading to challenges with tasks such as opening doors, using buttons, shoelaces, zips, keyboards, or pens. Dressing and self-care tasks that require coordination can be particularly difficult. Most individuals will require support in adulthood for tasks such as meal preparation (Sena et al., 2022) and will require support from physical therapy and occupational therapy.

Delayed language is evident in early childhood, but most individuals with Lowe syndrome can imitate words by the age of 2 and a half and can talk by the age of 7 (McSpadden, 2000). Most children with Lowe syndrome become toilet trained between the ages of 5 and 13, although this can be challenging due to constipation, which is thought to effect approximately 70% of individuals (Sena et al., 2022).

Almost all affected males have some degree of intellectual disability, with approximately 10-25% in the low to normal range (borderline), 25% in the mild to moderate range, and 50-65% in the severe to profound range of intellectual disability (Kenworthy et al., 1993).

Behavioural Aspects
Currently, there is little research regarding the social characteristics of individuals with Lowe syndrome. However, parents often report that their children enjoy social interaction but have difficulties interpreting social cues and knowing how to respond appropriately.

Research on parent reports of autistic traits found that 7 out of 10 parents reported that their child had autistic traits, and 3 out of 10 had a score suggestive of an autism diagnosis (Oliver et al., 2010). With regard to formal diagnosis, autism diagnosis has been reported

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in approximately 10% of individuals, and Attention Deficit Hyperactivity Disorder in 8.2% of individuals.

Repetitive behaviour is commonly reported in Lowe syndrome (Sena et al., 2022). In a study comparing the prevalence of parent-reported repetitive behaviours across different rare genetic syndromes, hand stereotypies and lining up behaviours were found to be higher in Lowe syndrome compared to other groups (Moss et al., 2008). Hand stereotypy has been noted in approximately 60% of individuals, on survey-based measures (Sena et al., 2022).

Emotional outbursts have been identified as common in Lowe syndrome, with aggression often being a core feature, including behaviours such as self-injury and destruction of property (Cressey et al., 2019; Sena et al., 2022). The most commonly reported triggers are changes in routine and unmet desires (e.g., wanting something that is not available) (Cressey et al., 2019). Some of these difficulties might be related to impaired cognitive processes such as emotional regulation and executive functioning, as similar links have been found in individuals with other rare genetic conditions (Chung et al., 2022; Rice, Woodcock, and Einfeld, 2018). Preliminary research at the University of Birmingham has found that individuals with Lowe syndrome often have difficulties delaying gratification, supporting that executive dysfunction within emotionally salient contexts likely plays an important role in reported emotional regulation difficulties (Waite et al., 2016).

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Ruth Roberts, Jess Hughes and Dr Jane Waite - Aston University - July 2023

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.

Behavioural characteristics

A recent study (Evans *et al.*, 2012) reported that the behaviors associated with MWS include a very high rate of oral behaviors (in particular, chewing or mouthing objects or body parts and grinding teeth), an increased rate of repetitive behaviors (such as switching lights on and off; flicking, tapping or twirling objects), and an under-reaction to pain. Other aspects of the MWS behavioral phenotype are suggestive of a happy affect and sociable demeanour. Despite this, those with MWS displayed similarly high levels of behavioral problems as a control group with a similar level of intellectual disability from other causes, with over 30% showing clinically significant levels of behavioral or emotional disturbance.

There are some reports of sleep disturbance in people with MWS (Evans, 2009).

Neuropsychological characteristics

Most people with MWS show a severe-profound level of intellectual disability (ID). However, as the syndrome was identified relatively recently, it is possible that more cases with milder phenotypes will be identified in the future. Motor skills are typically very delayed. While in many individuals, speech is absent or limited to a few words, some have greater success with signing or augmented and alternative communication systems (Evans, 2009). A study found that receptive language was superior to expressive on two measures of communication skills, though the difference in terms of age equivalents was only a few months (Evans, 2009).

Useful websites/associations for more information

- Website and international registryfor families affected by MWS: www.mowatwilson.org
- Australian 'Mowilsi' site: http://www.mowatwilsonsupport.org/
- French forum for families: http://smwf.forumactif.org/
- UK Support group: http://www.mowatwilsonsyndrome.org.uk/
- Italian support group: http://www.mowatwilson.it/

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Neurofibromatosis Type 1 (NF1)

Genetics
Autosomal dominant. Gene localised to 17q11.2. The gene product (neurofibromin) regulates the RAS-MAPK signaling pathway and is thought to suppress tumour formation by regulating cell division (Tidyman, 2009). A high spontaneous mutation rate means that about half of all cases arise in unaffected families.

Incidence/prevalence
About 1 in 2,700 births.

Diagnosis
In those people who do not have a parent with NF1, two of the following must be present to meet diagnostic criteria: (a) 6 or more café au lait macules (>5mm pre-pubertal, >15 mm post-pubertal), (b) axillary or inguinal freckling, (c) two or more neurofibromas of any type, or one plexiform neurofibroma, (d) optic pathway glioma, (e) two or more Lisch nodules, or choroidal abnormalities, (f) a distinctive osseous lesion, (g) a heterozygous pathogenic NF1 variant, with a variant allele fraction of 50% in apparently normal tissue.

In those people who have a parent with NF1, diagnostic criteria are met if one or more features above are present (Legius, Messiaen L, et al 2021).

Physical features
Physical manifestations of NF1 include café-au-lait spots, which occur in the first few years of life, intertriginous freckling, Lisch nodules (i.e. pigmented iris hamartomas or freckling in the iris), neurofibromas (i.e. benign Schwann cell tumors, divided into four types: (1) focal or diffuse cutaneous, (2) subcutaneous (under the skin), (3) spinal, and (4) nodular or diffuse plexiform neurofibromas, which develop from nerves and extend into surrounding structures, and which can transform into malignant tumours), optic pathway gliomas, and distinctive bone lesions (e.g., short stature or dystrophic scoliosis). Macrocephaly is common (Huijbregts, 2011).

Life expectancy
For most people with NF1 life expectancy is normal. However, the nature and severity of clinical features may change prognosis.

Brain abnormalities
Magnetic Resonance Imaging studies revealed many different abnormalities in the brains of NF1-patients. These include T2-hyperintensities (of which the nature is not yet known, and which do not seem to have clinical implications), volumetric abnormalities (mainly enlargements of subcortical structures), white matter abnormalities and differences in functional connectivity. The last three appear to be related to cognitive and social outcomes. The lifetime prevalence of epilepsy is reported to be 5.4%. (Bernando, 2020).

Behavioural characteristics
Many patients experience social and behavioural difficulties (Barton & North, 2004). These include communication difficulties and difficulties forming and maintaining friendships. Approximately 25% of children with NF1 meet the diagnostic criteria for autism, and another 25-30% exhibit the broader autistic phenotype (Chisholm, 2022). There is emerging evidence that the autism phenotype in NF1 is more homogenous than idiopathic autism, with reduced restrictive and repetitive behaviours compared to socio-communication difficulties. Cognitive deficits partly underlie the social dysfunction observed in NF1 (Huijbregts & De Sonneville, 2011). ADHD has been reported in 40—50% (Payne, 2021).

Cognitive characteristics
The global intellectual abilities of individuals with NF1 fall within a normal distribution, albeit towards the lower end of this distribution. More than half of children with NF1 show significant scholastic difficulties. Specific cognitive deficits occur in up to 80% of people with NF1, with attention, executive function and visual perception particularly affected.

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Treatment

People with NF1 should be reviewed at least annually and usually require multi-disciplinary care. Monitoring skin and bone changes (scoliosis) are important. Because of the multi-faceted nature of NF1, treatment is generally aimed at specific symptoms. For example, optic glioma are most often treated with chemotherapy (Ardern-Holmes & North, 2011). Also, trials have been performed with bisphosphonate drugs to treat bone abnormalities (Heervä *et al*., 2014), whilst results of studies using statins to treat social and cognitive impairments were inconclusive at best (Payne *et al*., 2016; Stivaros *et al*., 2018; Van der Vaart *et al*., 2013). Anti-seizure medications are used to treat epilepsy. Methylphenidate does seem to ameliorate some of the cognitive symptoms associated with NF1. Trials are currently underway with new medication (Lamotrigine) to improve cognitive and social functioning via increase of interneuron excitability (Omrani et al., 2015). To date, relatively little attention has been given to non-pharmaceutical interventions, whereas those that have been performed seem to have been relatively successful (e.g. Arnold *et al*., 2016).

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Stephan Huijbregts 2019
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Noonan Syndrome

First description

The first description of Noonan syndrome (NS) dates back to 1883, when a student named Kobylinski reported on a male patient with several phenotypical characteristics. In 1963, paediatric cardiologists Dr. Jacqueline Noonan and Dorothy Ehmke were the first to identify NS as a distinct syndrome in both male and female patients, with congenital heart defects, small stature, typical faces, skeletal malformations and mild developmental delay (Noonan & Ehmke, 1963; Noonan, 1968). John Opitz, one of Dr. Noonan's students, suggested the eponym and confirmed NS as a nosologic entity.

Associated conditions

NS is a genetically heterogeneous disorder, with different causative mutations in the RAS-MAPK pathway. Syndromes with shared pathogenetic mechanisms and clinical overlap with NS include Cardiofaciocutaneous (CFC) syndrome, Costello syndrome (CS), Legius syndrome (LS), Neurofibromatosis type 1 (NF1), Noonan syndrome with multiple lentigines (NS-ML; formerly called LEOPARD syndrome), and Noonan syndrome-like disorder with loose anagen hair (NS-LAH). They are grouped into the neurocardiofacialcutaneous syndrome family, or the RASopathies (Tartaglia *et al.*, 2011, Tajan *et al.*, 2018).

Genetics and molecular biology

NS is most often inherited in an autosomal dominant manner, although NS caused by a pathogenic variant in LZTR1 also can be inherited in an autosomal recessive manner. In 60% of patients with autosomal dominant NS, the condition is caused by a de novo mutation. In approximately 50% of patients with NS a missense mutation is found in the PTPN11 gene on chromosome 12 (12q24.13). Germline mutations in 16 other genes of the RAS-MAPK pathway are associated with NS and closely related disorders: SOS1 (10-13% of the cases), RAF1 (5-10%), RIT1 (5%), KRAS, NRAS, MRAS, BRAF, SHOC2, CBL, SOS2, RRAS, RASA2, MAP2K1, MAP2K2, LZTR1, and PPP1CB. In about 20 to 30% of the patients with a clinical diagnosis of NS, no mutation can be found yet (Allanson & Roberts, 2019; Grant *et al.*, 2018; Liao & Mehta, 2019; Motta *et al.*, 2020). Apart from these, preliminary evidence points at several other candidate genes such as RREB1 (Grant *et al.*, 2018; Kent *et al.*, 2020).

Incidence/prevalence

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

Physical features and natural history

Key characteristics are 1) short stature, 2) typical facial dysmorphology (wide-spread and down-slanting eyes, drooping eyelids, and low-set, and posteriorly rotated ears with a thickened helix), and 3) congenital heart defects (pulmonary valve stenosis, hypertrophic cardiomyopathy, and atrial septal defects are most common). Some additional features are variable developmental delay, neonatal feeding difficulties, failure to thrive, hematologic and ectodermal anomalies, skeletal anomalies (e.g., chest deformity), lymphatic dysplasia, cryptorchidism, ocular abnormalities, widely spaced nipples, and a webbed neck. However, these characteristics are not seen in all patients with NS, phenotypical expression is highly variable and often milder in adulthood than in youth (Allanson & Roberts, 2019; Noonan, 2005). The diagnosis is primarily made on clinical grounds, by observation of cardinal features. The most widely used scoring system was developed in 1994 and updated and validated in 2010 (Van der Burgt *et al.*,1994; DYSCERNE-Noonan Syndrome Guideline Development Group, 2010). Life expectancy for patients with NS is fairly normal, unless there are major complications of heart disease. Premature delivery is the main source of morbidity.

Behavioural characteristics and psychopathology

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

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

Neuropsychological characteristics

Neuropsychological findings show intelligence scores in a wide range, with a mildly lowered average intelligence. Language and motor development are often delayed. In children, a highly variable cognitive profile has been found, with indications for impairments in visual processing and language development, varying reports of memory problems, attention problems, and suboptimal planning and organisational skills (Pierpont 2016). These cognitive impairments might explain the anecdotally reported learning problems and need for special education. While cognitive problems are frequently present in childhood, cognition in adults with NS is mainly characterised by a lowered speed of information processing. As described above, social cognitive functions (recognising and expressing emotions) may be impaired as well (Wingbermühle *et al.*, 2012b). .

Available guidelines for assessment/treatment/management

The specific problems that patients with NS may encounter in daily life appear to result from a complex interaction between genetic, somatic, cognitive, psychological, and environmental factors. Therefore, a multidisciplinary approach and intensive collaboration between clinical geneticists, cardiologists, paediatricians, clinical neuropsychologists, physiotherapists, and speech therapists, among others, is necessary to treat patients with NS as best as possible. Moreover, NS is a lifelong developmental disorder, which poses different challenges in different stages of life. Repeated individual clinical and neuropsychological assessment is advised throughout the lifespan, especially at crucial moments in the development and when problems occur. The recommended multidisciplinary approach and life-long follow-up may be formalised in centres of expertise for patients with NS and other RASopathies. Specific recommendations for the management of patients with NS at different stages of their lives can be found in the international clinical guidelines on Management of Noonan syndrome from the Noonan Syndrome Guideline Development Group (DYSCERNE, 2010).

More information

- www.ncbi.nlm.nih.gov/omim/163950 For the information on NS in OMIM, an online database of human genes and genetic disorders.
- www.noonansyndrome.org.uk For the Noonan syndrome support group Inc.
- rasopathiesnet.org/wp-content/uploads/2014/01/265_Noonan_Guidelines.pdf For the Noonan Syndrome Clinical Management Guidelines.

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Phelan-McDermid Syndrome – (22q13.3 Deletion Syndrome)

Alternative names

Previously known as 22q13.3 Deletion Syndrome, the condition is now commonly called Phelan-McDermid syndrome (PMS). Some individuals have a pathogenic variant of the gene *SHANK3*, but no detectable deletion in 22q13.3. It should be noted that individuals with ring chromosome 22 commonly have a deletion of the distal part of chromosome 22.

History of the syndrome

Ring chromosome 22 was described as a possible deletion syndrome in 1968 (Weleber, Hecht, & Giblett, 1968), and a description of 'pure' partial monosomy syndrome was published by Watt et al. (1985). In 1992, Phelan et al. published an article with a detailed description of a case with 22q13 deletion (M. C. Phelan et al., 1992). Two subsequent reports highlighting the role of *SHANK3* in explaining the phenotype of the syndrome were published by Bonaglia et al.(2001) and Luciani et al. (2003). The main characteristics of the PMS phenotype are described below but diagnosis can only be confirmed by genetic analysis. Previously, it was thought that involvement of *SHANK3* was necessary for diagnosing the syndrome, but a recent article has proposed a nomenclature that specifies PMS as being either PMS-*SHANK3* related or PMS-*SHANK3* unrelated (K. Phelan et al., 2022).

Incidence/prevalence

Figures on prevalence are limited; current estimates are around 1/30 000 live births but the syndrome is probably underdiagnosed. Studies in populations with intellectual disability (ID) have reported prevalence figures of PMS ranging from 0.25-3.33 %, with the highest estimates associated with more severe-profound ID (Schön et al., 2023).

Physical features and natural history

The phenotype and natural history of the syndrome are variable. More than 75% of individuals have neonatal hypotonia which may persist into childhood, and motor abnormalities are common (Frank, 2021; K. Phelan, Rogers, & Boccuto, 2018; Schön et al., 2023). There may be minor morphological features such as large and fleshy hands, long eyelashes or large and prominent ears. Multiple comorbidities can occur throughout the lifetime. Gastrointestinal problems such as gastroesophageal reflux, cyclic vomiting, constipation or diarrhoea, as well as chewing and swallowing problems and frequent airway infections are common in children (K. Phelan et al., 2018). Epilepsy, involving different types of seizure, can start at any age (Frank, 2021). One study reports that the life time prevalence of epilepsy may be as high as 60% (de Coo, Jesse, Le, Sala, & Bourgeron, 2023).

Cognitive development, behavioural aspects and psychiatric disorders

PMS is characterised by global developmental delay with moderate to profound ID. Marked speech impairment is present in the majority of cases, and alternative and augmentative communication is recommended (Vogels, Droogmans, Vergaelen, Van Buggenhout, & Swillen, 2021). Autism or autism like behaviour is common and is reported in up to 70-80% of individuals with PMS (van Balkom et al., 2023; Vogels et al., 2021). Bipolar disorder and (periodic) catatonic symptoms seem to be particularly prevalent (Verhoeven, Egger, & de Leeuw, 2020). Autism can be identified by the use of the same instruments in PMS as in idiopathic autism, and similarly ID and level of ID can be identified in PMS by the same assessment methods as in individuals without PMS. (Vogels et al., 2021). Many individuals have disturbed sleep. Reduced response to pain is common, and this poses a risk for somatic issues, such as constipation, ear infections, gastroesophageal reflux or dental problems to be diagnosed late or remain unnoticed (Walinga, Jesse, Alhambra, & Van Buggenhout, 2023). Disturbed heat regulation with a tendency to overheat and decreased perspiration are also frequently reported (Frank, 2021).

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Regression

Neurodevelopmental regression, with of loss previously acquired skills, is a key feature of PMS (Dille, Lagae, Swillen, & Buggenhout, 2023; Frank, 2021; Reierson et al., 2017). Regression may involve loss of language/communication, motor or adaptive skills. Both sudden and gradual onset of regression at different ages have been reported. There is no apparent cause in most cases, but symptoms may appear after acute events such as infections, prolonged seizures, or environmental changes. Acute onset of psychiatric symptoms such as catatonia, hallucinations and bipolar disorders can occur in adults. Dille et al. (2023) identified a distinct pattern of developmental regression with four stages across the lifespan: (I) Acute onset of language regression in children, (II) followed by a plateau, (III) severe acute-onset psychiatric symptom in adults/adolescents and (IV) late neuromotor deterioration. The last stage is often preceded by an acute trigger or event such as severe sickness, hormonal shifts, and psychosocial stress. Diagnostic identification and appropriate treatment of psychiatric and somatic disorders are essential when regression occurs.

Genotype Phenotype correlations

SHANK3 is considered the major gene for PMS, and this gene is closely linked to autism symptoms. In general, a smaller deletion is associated with higher cognitive and adaptive levels. Previously, it had been thought that the clinical features were apparent in all individuals with a non-mosaic 22q13.3 deletion, but it has been reported that small deletions of *SHANK3* may have variable penetrance suggesting that some individuals may have compensating mechanisms (Tabet et al., 2017). It should be noted that some individuals seem to have additional copy number variations (CNVs) such as 16p11.2 and 15q11q13 contributing to the phenotype (Tabet et al., 2017). Neurofibromatosis type 2 (NF2) pathogenic variants lie adjacent to the region deleted in PMS, and individuals with ring chromosome 22 have a specific risk of developing (NF2). These individuals should be followed as if they had an affected parent (K. Phelan et al., 2018).

Available guidelines

European Journal of Medical Genetics have published European consensus guidelines for PMS, which were supported by The European Reference Network ITHACA (Intellectual disability, TeleHealth, Autism and Congenital Anomalies) (van Ravenswaaij-Arts et al 2023).

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Prader-Willi Syndrome (PWS)

First description

Prader-Willi syndrome (PWS) was first described in 1956 by Prader, Labhart and Willi.

Genetics and molecular biology

PWS results from the absence of expression of the paternal allele of paternally expressed/maternally imprinted genes at the chromosomal locus 15q11-q13 (the PWS critical region). The commonest genetic mechanisms leading to PWS are: a) a de novo deletion at the PWS critical region on the chromosome of paternal origin (60%) and b) maternal uniparental disomy (mUPD) of chromosome 15 where both chromosomes are derived from the mother (36%) (Butler *et al.* 2019). Other rarer causes of PWS include imprinting centre defects (4%) and unbalanced translocations. A number of paternally expressed/maternally imprinted genes have been identified within the PWSCR of which the largest is SNRPN (containing the imprinting centre) which codes for a small nuclear ribosomal protein involved in the control of synthesis of proteins related to hypothalamic function. Imprinted and non-imprinted genes are found within the deleted region; SNORD 116, MAGEL 2 and IPW being the genes whose absence of expression at the locus 15q11-13 are considered central to PWS. As yet, no single gene mutation has been identified as a cause of PWS, other than a mutation of the imprinting centre which itself influences the expression of several genes.

Despite significant advances in genetic testing, diagnosis is usually made clinically, and can be delayed until later in childhood. Mahmoud *et al.* (2019) carried out a feasibility study which showed that newborn screening was accurate, able to differentiate genetic subtypes, and could lead to earlier intervention with better outcomes.

Incidence/prevalence

The estimated birth incidence is 1 in 29,000 and the prevalence is 1 in 52,000 (Whittington *et al.* 2001).

Natural history

The early phenotype is characterised by severe hypotonia after birth, which affects the infant's ability to suck, resulting in feeding problems and consequent failure to thrive which may necessitate gavage feeding. Hypothalamic dysfunction leading to growth hormone and steroidal sex hormone deficiency may account for several features of PWS (Goldstone 2004), including the control of birth processes, short stature, hypogonadism, aberrant body temperature control and daytime hypersomnolence. Characteristic facial features include dolichocephaly, narrow bifrontal diameter, almond shaped palpebral fissures, small down turned mouth and thin upper lip (Holm *et al.* 1993).

The onset of the striking characteristic of hyperphagia separates the early and late phenotype. Between the ages of 1 and 6 years, the child develops a propensity for eating which, if left unaddressed, can result in obesity and medical problems. The hyperphagia is considered to be hypothalamic in origin, and caused by failure of the normal satiety response following food intake (Holland *et al.* 1993; Hinton *et al.* 2005). Infertility remains almost universally present although there are rare reports of children being born to females with PWS.

Behavioural and psychiatric characteristics

The main behavioural techniques used to address hyperphagia include preventing access to food e.g. by locking cupboards, low calorie diets, all members of the household having the same diet and ongoing education about the risks of overeating. Appetite suppressants and gastric banding have not been shown to be useful. Octreotide has been shown to decrease concentrations of ghrelin in adolescents with PWS, but does not reduce appetite or BMI (De Waele *et al.* 2008).

Aside from the over-eating, the most common problem behaviours are temper tantrums, mood swings which do not fulfil criteria for a defined psychiatric disorder; ritualistic and repetitive behaviours; and self-mutilation in the form of skin-

picking. Evidence suggests that modulation of the glutaminergic pathway may reduce the compulsive behaviours; oral N-acetylcysteine was found to reduce skin picking, although participants with PWS were not compared with a control group (Miller & Angulo 2013).

A comprehensive study of 101 participants with PWS found that temper outbursts decreased in frequency with age, while the duration of outbursts increased. Provocations fitted in to three themes: goal blockage, social injustice, and difficulty dealing with change. Medications were prescribed, but were not found to be particularly effective (Rice *et al.* 2018).

Relative to others with intellectual disability, people with PWS are more likely to exhibit severe problem behaviours (Dykens *et al.* 1997). Obsessional traits occur commonly, in particular needing to ask or tell, requiring routines, hoarding and repetitive questioning (Clarke *et al.* 2002). It has been found that people with PWS who are exposed to routines for longer before a change are more likely to engage in temper outburst behaviours (Bull *et al.* 2014).

The mUPD genetic subtype of PWS is strongly associated with the development of affective psychosis (Boer *et al.*2002). In a UK-wide sample of 119 adults with PWS, 62% of those with mUPD had a diagnosis of psychotic illness compared with 17% of those with a deletion (Soni *et al.* 2008). Atypical symptoms such as hypersomnia and confusion were seen, and those with mUPD had a more severe, difficult-to-treat illness with a poorer outcome compared to those with a deletion (Soni *et al.* 2007). However, once stability has been achieved in psychotic illness, recurrence rates are low (Larson *et al.* 2013). Dementias are now being documented as individuals survive into old age (Sinnema *et al.* 2010). Autism has been reported (Veltman *et al.* 2004); candidate genes for autism have been located within the 15q11-q13 region and there is evidence that those with mUPD may be more severely affected than those with a deletion (Ogata *et al.* 2014).

A review of the literature in order to understand how best to conceptualise behaviours and abnormal moods states associated with PWS was undertaken by Whittington & Holland (2018). Many behaviours such as eating behaviour, obsessive compulsive behaviours and skin picking, appear to have a strong genetic aetiology, whereas depression and psychosis have both genetic and environmental aetiologic components. The authors caution against using standardised diagnostic labels to describe common PWS behaviours (e.g. repetitive ritualistic behaviours typical in PWS are not equivalent to those seen in OCD) as this may lead to inappropriate treatments.

Neuropsychological characteristics

The full scale IQ is usually in the mild intellectual disability range, and a mean downward shift of approximately 40 points compared to the general population is seen (Whittington *et al.* 2004). Those with mUPD tend to have better verbal skills and those with a deletion have better visuo-spatial skills. Also seen are poor short-term memory, deficits in sequential processing, poor socialisation skills, deficits in comprehension, abstract reasoning, recognising emotions and appreciating the concept of time.

Neuroimaging findings

Functional and anatomical studies have implicated a combination of subcortical and higher order structures in PWS, including those involved in processing reward, motivation, affect and higher order cognitive functions (Manning & Holland 2015).

A study by Lukoshe *et al.* (2013) looked at high resolution structural magnetic resonance imaging in children with confirmed PWS. All children with PWS showed signs of impaired brain growth. Those with mUPD showed signs of early brain atrophy. In contrast, children with a deletion showed signs of fundamentally arrested, although not deviant, brain development and presented few signs of cortical atrophy. The authors suggest that there are divergent neurodevelopmental patterns in children with a deletion versus those with mUPD.

Increased brain age was seen in adults with PWS who underwent MRI scanning (Azor *et al.* 2019). This was independent of high BMI, or use of growth and sex hormones, and may reflect premature brain aging or abnormal brain development.

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Physical health and endocrine

The most prevalent physical health problems in people with PWS are scoliosis, respiratory problems, dermatological lesions, hyperlipidaemia, hypothyroidism, Type 2 diabetes mellitus and lymphoedema (Laurier *et al.* 2014).

Growth hormone supplementation can increase height and the rate of growth, decrease mean body fat, improve respiratory muscle function and physical strength and improve facial dysmorphism. However, after cessation of growth hormone therapy, BMI can increase again, and long term therapy may be indicated (Oto *et al.* 2014). Furthermore, cessation of growth hormone therapy may lead to successive deterioration in behaviours in children with PWS (Bohm *et al.* 2014).

A study by Cohen *et al.* (2014) showed that central sleep apnea with associated oxygen desaturations is more prevalent in infants compared with older children with PWS. The authors found that supplemental oxygen was efficacious in treating central sleep apnea in infants and advised routine sleep surveillance for all children with PWS with consideration given to oxygen therapy.

Symptoms of constipation are common in people with PWS with up to 40% fulfilling defined criteria for constipation in a study by Kuhlmann *et al.* 2014. These symptoms cannot be explained by abnormal eating habits. Gastrointestinal transit times are also increased compared with the general population and may in part be related to poor muscle tone. Studies have shown that people with PWS produce less saliva and have a high risk of choking. A pilot study by Gross *et al.* (2014) showed that food was visualised on x-ray, lodged in throats, but the people with PWS were unaware of it.

Osteoporosis, osteopenia and fractures are relatively common in people with PWS. Growth hormone treatment can improve bone size and strength but not bone mineral density in people with PWS (Longhi *et al.* 2015).

Useful websites/associations for more information

- PWS Association UK: www.pwsa.co.uk
- PWS Association USA: www.pwsausa.org
- IPWSO (International PWS Organisation): www.ipwso.org
- Online Mendelian Inheritance in Man (OMIM): www.omim.org

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Rubinstein-Taybi Syndrome (RTS)

Prevalence

Although prevalence estimates have varied it is thought that the most accurate estimate is approximately 1 in 100,000 to 125,000 live births.

Genetics

Genetic markers are found in around 65-70% of cases and some individuals are diagnosed through clinical characteristics alone. RTS can be divided into two types: RTS1 and RTS2. These types are linked to heterozygous pathogenic changes or re-arrangements in the genes CREBBP and EP300, respectively. Both CREBBP and EP300 genes encode paralogous transcriptional coactivators with Lysine Acetyl Transferase Activity. CBP and p300 proteins are vital in initiating transcription. There are only a small number of reports of the clinical and behavioural features of RTS2, and these reports have indicated individuals are often more mildly affected, particularly in terms of the skeletal features and degree of intellectual disability.

Physical features

The physical characteristics associated with RTS have been well documented and include broad thumbs and toes, microcephaly, excessive hair growth and dental abnormalities (including narrow high-arched palate). The classical facial appearance changes with age. Descriptions in adults typically include low hanging columella, eyes with downward slanting palpebral fissures, long eyelashes, thick eyebrows, and a small mouth. Feeding problems are often present at birth, with descriptions of poor appetite, vomiting and failure to thrive during infancy, followed by enhanced appetite and weight gain in adolescence. Other health problems include renal abnormalities, constipation, recurrent upper respiratory infections, undescended testes in males and keloids.

Behavioural characteristics

Although still in its infancy, the literature outlining the behavioural phenotype of RTS is growing. In 2022, the literature was reviewed systematically, to describe the patterns of behaviour in RTS. The two most frequently noted characteristics relate to social behaviour and repetitive behaviour. Reports have described those with RTS as "overfriendly" and "happy" individuals who "love adult attention" and "know no strangers". Such descriptions have led to the suggestion that individuals with RTS may show some enhanced, or preserved, social communication skills when compared to those with other causes of ID. Stereotyped behaviours such as rocking, spinning, and hand flapping, appear to be common. Other repetitive behaviours noted in around three quarters of individuals with RTS include an adherence to routine and an insistence on sameness.

Studies have also described sleeping difficulties, a tendency for individuals to be "emotional" and "excitable", and "stubbornness". The presence of ADHD-type behaviour, such as impulsivity and hyperactivity, has also been noted. Studies have commented on challenging behaviour in individuals with RTS, including aggressive behaviours and self-injurious behaviours, although evidence that these are more common in RTS than in ID generally is lacking.

Emotional Characteristics

Despite some studies showing social competency and social skills, other research has indicated that individuals with RTS demonstrate higher levels of social anxiety than those with Down syndrome across a range of social situations with both familiar and unfamiliar adults. Adolescents with RTS have been shown to be more likely to exhibit greater anxiety symptoms than infants and children with RTS. It has also been suggested that individuals with RTS may be at increased risk of mood instability and emotional outbursts as they get older. More research is needed to explore the emotional and psychiatric characteristics of individuals with RTS.

Cognitive characteristics

Intellectual disability (ID) is an associated characteristic of RTS. Although estimates regarding the degree of ID have varied across studies, and there is a wide range of IQs within the syndrome, it is thought that

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most individuals lie within the moderate range. Genetics studies have started to link the molecular abnormalities to cognitive dysfunction in RTS. The CREB binding protein implicated in RTS has been shown to underlie long term memory formation and consequently it has been suggested that ID may be related to impaired long-term memory.
Preliminary work assessing social cognition in RTS indicates some 'precursor' social cognitive abilities are intact but there may be subsequent deficits in later developing Theory of Mind. In addition, there is emerging evidence that executive function abilities may be compromised in RTS relative to mental age and that these difficulties may be related to repetitive behaviours observed in the syndrome.

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Updated July 2023 – Courtney Greenhill & Jane Waite

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.*,

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2013). Developmental regression in RTT remains still a puzzling and complex phenomena (Einspieler & Marschik, 2019; Smeets, Townend, & Curfs, 2019; Zhang *et al.*, 2019).

One of the first noticeable signs is a deceleration in head growth. Other symptoms include loss of motor and communication skills, namely the loss of verbal language and purposeful hand use, accompanied by stereotypic hand movements (the handwashing/clapping noticed by Andreas Rett). Additional features include abnormal gait and an inability to walk; abnormal breathing and sleep patterns, altered muscle tone, scoliosis, growth retardation and small cold hands and feet (Neul *et al.*, 2010). Poorly regulated central autonomic function leads to disturbed cardio-respiratory control with episodes of breath-holding, shallow breathing, hyperventilation and valsalva breathing. Epilepsy is present in 60%–80% of individuals (Operto, Mazza, Pastorino, Verrotti, & Coppola, 2019). Early hypotonia gives way to hypertonia with the risk of contractures and episodes of dystonia are common. Abnormal oral movements may make feeding difficult. Gastric reflux, aerophagy and constipation are common.

Communicative, cognitive and behavioural characteristics

Anxiety and mood disorders are frequently reported. Perhaps the most significant factor influencing quality of life for individuals with RTT and their families, however, is the severe limitation in their ability to communicate through conventional channels such as speech and hand signs/gestures (Cass *et al.*, 2003). To what extent apraxia rather than any deeper language and cognitive impairments influences these limitations, is a subject for ongoing debate. In general, older studies suggest that most individuals with RTT operate at pre-linguistic, pre-intentional levels of communication. Several studies also point to low levels of language comprehension and cognitive functioning (Berger-Sweeney, 2011), especially when standardised receptive language, IQ or adaptive behaviour tests are employed. In contrast, parents frequently report that their children know more than they are able to express or to demonstrate on assessment (Bartolotta, Zipp, Simpkins, & Glazewski, 2011; Urbanowicz, Leonard, Girdler, Ciccone, & Downs, 2014) and there is growing (anecdotal) evidence that the population of individuals with RTT spans a broader range of cognitive ability than previous thought. They are universally recognised as engaging in "intense eye communication" (Neul *et al.*, 2010) (p. 946) and many parents and professionals advocate an approach of "presumed competence". There is growing interest in the potential benefits that eye gaze/eye-tracking technologies can offer to individuals with RTT (Townend *et al.*, 2016). This has led to calls for the development of more objective eye gaze/eye-tracking based cognitive and receptive language assessments, which can be used to validate parental reports (Byiers & Symons, 2013; Urbanowicz *et al.*, 2014)..

Differential diagnosis

Clinical criteria for the diagnosis of classic RTT and its atypical variants e.g. Preserved Speech Variant (Renieri *et al.*, 2009) were revised in 2010 by members of the Rett Search consortium (Neul *et al.*, 2010). Following clinical identification by core and supportive consensus criteria, the diagnosis may be confirmed by genetic analysis.

Historically, individuals with RTT were labelled as having an "autism spectrum disorder" (ASD) (Young *et al.*, 2008), however, RTT was removed from the umbrella of ASD in the 2013 publication of DSM-V. While individuals with RTT pass through an autistic-like phase during regression, many regain social awareness and are especially noted for their sociability. Those with milder atypical forms of RTT (e.g. PSV) may continue to display features of ASD (Kaufmann *et al.*, 2012).

Management

In 2007 Bird and colleagues first demonstrated that the symptoms of RTT could be reversed in mice (Guy, Gan, Selfridge, Cobb, & Bird, 2007). Since then much research has been devoted to both the treatment and potential cure of RTT (although this continues to be quite some way off) as well as the development of more functional therapies which address day to day care and seek to enhance the participation and quality of life of individuals living with this rare disorder.

Due to their complex physical and psychological needs individuals with RTT and their families require

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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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SATB2-Associated Syndrome

First description and alternative names

Glass et al. (1989) first described a male with a 2q32.2-q33.1 deletion that included the *special AT-rich sequence-binding protein 2 (SATB2)* gene, subsequently, the name 'Glass syndrome' (OMIM #612313) was proposed.

Since 1989, varying genetic alternations to the *SATB2* gene have been documented to produce a relatively consistent phenotype, independent of the underlying pathogenic variant. Phenotypic differences are thought to relate to differences in severity rather than the system affected (Zarate & Fish, 2017). *SATB2*-associated syndrome (SAS) was therefore designated as a single clinically recognised syndrome in 2014, in an effort to unify the terms for different alterations affecting the *SATB2* gene (Döcker et al., 2014).

In addition to Glass Syndrome, alternative names include 2q32 Deletion Syndrome, 2q33.1 Microdeletion Syndrome, and Chromosome 2q32-q33 Deletion Syndrome.

Genetics

The SAS phenotype is associated with alterations causing functional haploinsufficiency of the *SATB2* gene (OMIM #608148) located on chromosome 2q33.1 (Cotton et al., 2020; Zarate & Fish, 2017). Alterations can result from a variety of molecular mechanisms, such as missense (31%), nonsense (24%), frameshift (20%), and intragenic deletion (14%) (Zarate et al., 2019).

SAS is an autosomal dominant disorder (an abnormal gene from one parent can cause SATB2). For most individuals, SAS is reported to occur as the result of a de novo genetic alteration; however, instances of mosaicism (where a percentage of cells in the body are affected by the genetic alteration) have been documented (Leoyklang et al., 2007; Zarate et al., 2019).

The *SATB2* gene is a regulator of several gene regulatory networks (GRNs) and has critical roles in multiple developmental processes, including skeletogenesis (skeleton formation), osteogenesis (bone formation) and craniofacial patterning (skull and facial formation) (Britanova et al., 2006; Dobreva et al., 2006; Gong et al., 2014). The *SATB2* gene is also expressed in the developing cortex and other tissues including the kidney and gut (Alcamo et al., 2008; Britanova et al., 2008). The presence of intellectual disability and speech delay/absence in individuals with SAS has been attributed to the essential role of the *SATB2* gene in neuronal connectivity (Döcker et al., 2014).

Incidence/prevalence

The true prevalence of SAS is unknown. However, SAS is estimated to occur in approximately .24-.30% of individuals with an undiagnosed intellectual disability or developmental delay (Bengani et al., 2017; Zarate et al., 2018).

Physical features and natural history

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

Minor facial dysmorphisms have been described in individuals with SAS, including a thin upper lip, flat philtrum (grove between the upper lip and nose), prominent chin, micrognathia (small lower jaw), abnormal dentition, deeply set eyes, low-set ears, and a prominent forehead or high anterior hairline (Zarate & Fish, 2017; Zarate et al., 2017; Zarate et al., 2018). Facial change with age is reported, with progressive coarsening of facial features in older individuals (Zarate et al., 2018).

Craniofacial and dental abnormalities are characteristic of individuals SAS. Frequently reported palatal abnormalities include cleft palate and high-arched palate, while bifid uvula (split soft palate at the back of the throat) has been reported in a small number of individuals (Zarate et al., 2019). Dental abnormalities are present in all individuals and become apparent from one year of age (Zarate et al., 2018). Delayed development of the mandibular second premolars (premolars on the lower jaw) or roots of the permanent teeth, dental crowding with malocclusion (misalignment of the upper and lower teeth),

abnormal tooth shape, and multiple odontomas (benign tumours linked to tooth development) are reported (Kikuiri et al., 2018; Scott et al., 2018; Zarate et al., 2018). Sialorrhea (drooling or excessive salivation) is often present (Zarate et al., 2018).

Feeding difficulties are common during infancy and into early childhood and have been attributed to the combination of craniofacial abnormalities and hypotonia (low muscle tone). Many infants are of low birth weight and low weight often persists. Tube feeding is often required in infancy, and this process may continue for several years (Zarate et al., 2019; Zarate et al., 2018). Gastrointestinal difficulties are reported, including constipation and/or gastro-oesophageal reflux (Zarate et al., 2021; Zarate et al., 2017).

In some individuals with SAS, skeletal abnormalities have been reported, including scoliosis, tibial bowing (bowing shin bone), pectus excavatum (sunken breastbone), and abnormal bone mineralisation (Mouillé et al., 2022; Zarate et al., 2018). Individuals may experience difficulties with movement and balance (Zarate & Fish, 2017; Zarate et al., 2017). An average age of 25.5 months has been reported for individuals taking their first steps (Zarate et al., 2019).

Clinical seizures are present in some individuals with SAS; however, subclinical seizures with abnormal electroencephalogram (EEG) activity have also been observed (Zarate & Fish, 2017; Zarate et al., 2017). Abnormal EEG activity has included abnormal wakefulness (staring spells, disorientation episodes, and/or laughing fits), slow background, and/or epileptiform discharges (Lewis et al., 2020; Zarate et al., 2018).

Other health problems include otitis media (middle ear infections), visual problems (e.g., strabismus (squint) and refractive errors), genitourinary problems and cardiac defects (Bissell et al., 2022; Zarate & Fish, 2017; Zarate et al., 2021; Zarate et al., 2017).

Behavioural characteristics

Individuals with SAS often display a happy disposition or friendly demeanour, with heightened motivation for social contact (Zarate et al., 2017; Zarate et al., 2018). However, this may be offset by the presence of behaviour that challenges, which are outlined within the S.A.T.B.2 diagnostic acronym (Zarate & Fish, 2017; Zarate et al., 2017). High rates of self-injury (43%), property destruction (49%) and aggression (77%) are reported (Bissell et al., 2022). Rates of self-injury and aggression in SAS are comparable to rates in non-syndromic autism and Angelman syndrome, while rates of property destruction are lower in SAS compared with non-syndromic autism and Angelman syndrome (Bissell et al., 2022).

Self-injurious behaviours, aggressive behaviours, and destruction of property behaviours are present in children, adolescents, and adults with SAS (Bissell et al., 2022). Behavioural changes with age are also indicated from clinical observations suggesting temper outbursts in childhood, with more physical acts of aggression emerging in adolescence and adulthood (Zarate et al., 2017).

An association between SAS and autism characteristics has been consistently reported (Lewis et al., 2020; Zarate & Fish, 2017; Zarate et al., 2021; Zarate et al., 2019). Bissell et al. (2022) report 46% of individuals met cut-off scores suggestive of autism spectrum disorder (ASD) according to the Social Communication Questionnaire (Berument et al., 1999). This concurs with rates of ASD (46%) reported by Zarate et al. (2021). Reported rates of ASD in SAS are comparatively high on screening measures compared to the prevalence of ASD in other syndrome groups associated with autism and intellectual disability (Richards et al., 2015). Fine-grained analyses reveal a distinct profile of autism characteristics and repetitive behaviour in SAS relative to individuals with non-syndromic autism. Key findings include convergent levels of compulsive behaviour and insistence on sameness, and differences in reciprocal social interaction and restrictive, repetitive, and stereotyped behaviour (Bissell et al., 2022). Impulsivity and hyperactivity are also frequently reported as behavioural features of SAS (Bissell et al., 2022; Lewis et al., 2020; Zarate & Fish, 2017; Zarate et al., 2019).

Sleep difficulties are common in children and adults with SAS and are reported to occur in between 50% and 75% of individuals. Difficulties include problems with initiating and maintaining sleep, sleep-wake transitions, early awakening, and sleep-breathing

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

Atypical sensory sensitivity has been described in some individuals. This has included reports of hypersensitivity to sound and touch (Balasubramanian et al., 2011; Tomaszewska et al., 2013; Zarate & Fish, 2017) and reports of an atypically high pain-threshold (Rosenfield et al., 2009; Scott et al., 2019; Zarate et al., 2017).

Emotional characteristics

Despite the frequent presence of a jovial disposition in SAS (Zarate et al., 2017; Zarate et al., 2018), individuals may show a propensity towards internalising problems such as anxiety and depression (Balasubramanian et al., 2011; Cotton et al., 2020; De Ravel et al., 2009; Kumar & Zarate, 2020; Van Buggenhout et al., 2005). High rates of anxiety (37%) have been reported by caregivers in a study with adolescents and adults (Zarate et al., 2021). However, lower rates of general anxiety (17%) have been reported in a larger sample including children and adults (Bissell et al., 2022), based on caregiver-report using the Anxiety Depression and Mood Scale (ADAMS; Esbensen et al., 2003). Bissell et al. (2022) further report that 13% of individuals with SAS met cut-off for depressed mood on the ADAMS. Mental health and emotional characteristics are under-researched in SAS; this may be partly attributable to difficulties in the measurement of emotional characteristics in individuals with impaired expressive communication.

Cognitive characteristics

SAS is universally associated with developmental delay and intellectual disability with delayed language acquisition (Zarate et al., 2018). Severe to profound intellectual disability is reported in over 50% of individuals with the syndrome (Zarate & Fish, 2017). Almost all individuals with SAS require assistance with activities of daily living and ongoing care (Zarate et al., 2021).

Communication deficits are observed in both receptive and expressive language (Thomason et al., 2019). Recent papers exploring communication found that fewer than ten words were spoken by 84% of individuals, and 42% of individuals were non-verbal (Zarate et al., 2019). Reported methods of alternative communication include the use of gestures, signs, and/or alternative augmentative communication devices; however, alternative communication skills are limited (Thomason et al., 2019). Marginal strengths in receptive and non-verbal communication are reported compared to spoken language (Zarate et al., 2021; Thomason et al., 2019).

Genotype x phenotype correlations

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

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

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

Life expectancy

Little is known about the life expectancy of individuals with SAS, although current research studies have included participants aged up to 37 years (Bissell et al., 2022; Zarate et al., 2021).

Useful websites/associations for more information

- SATB2 Gene Foundation USA: www.satb2gene.org
- SATB2 Gene Trust UK: www.satb2gene.org.uk
- SATB2 Europe: www.satb2europe.org
- SATB2 Gene Foundation Australia: www.satb2.org.au

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Triple-X Syndrome (47,XXX; TXS)

First description and alternative names

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

After the first description there was a period of research in biased populations, e.g., in institutes for mentally retarded, asylums and forensic psychiatric hospitals (Olanders, 1975). In 1974 it was decided to screen 200,000 newborns for chromosomal disorders in several hospitals. TXS cases in this study have been evaluated several times for at least 20 years. These newborn-screening studies yielded unbiased data (Robinson et al., 1990). After 1990, two of these hospitals (Denver and Edinburgh) published follow-up data in young adults (Otter et al., 2010). Recent studies from other research groups published data from biased groups of cases (Wilson et al., 2019). Other studies reported results of mixed sex groups of participants and mixed groups of sex chromosome trisomies (47,XXX, 47,XXY, and 47,XYY). Some of the 47,XXY cases have received testosterone treatment, and others did not (Bouw, Swaab, Tartaglia, et al., 2022). These issues should be considered in the appraisal of study results.

Genetics and molecular biology

In TXS, there is an extra X chromosome in all cells or, in mosaic cases, in almost all cells. Most of the cases are diagnosed through prenatal diagnostic examinations. Other girls and women may be diagnosed postnatally because of infertility/recurrent abortions, atypical development or when a family member appears to have a genetic condition (Otter et al., 2021).

In 46,XX females the extra X chromosome is silenced through lionization. The extra X chromosome in TXS is also silenced. In 46,XX females one-third of the genes on the X chromosome escape silencing (Migeon, 2007), and diverse patterns of X chromosome regulation have been shown during development, and in various tissues and diseases (Deng et al., 2014; Loda et al., 2022). The so-called 'late-replicating' X chromosome is the second X chromosome in 46,XX women. In TXS, there is another late-replicating chromosome, so replication time increases during each cell division (Barlow, 1973). The extra X chromosome also influences the nuclear architecture and epigenetic processes (Jowhar et al., 2018; Kelkar & Deobagkar, 2010). Whether incomplete silencing of the extra X chromosome, the prolonged cell cycle during division or epigenetic phenomena are relevant during development in 47,XXX, requires further research (Wainer-Katsir & Linial, 2019). Knowledge about sex differences in the brain (Raznahan & Disteche, 2021) and modern technology (Tallaksen et al., 2023) may help elucidate the biological relationship between the extra X chromosome and behavioural patterns in TXS.

Incidence/prevalence

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

Physical features and natural history

Tartaglia et al. (Tartaglia et al., 2010) reviewed the physical findings in TXS. Since most of these findings (such as clinodactyly, epicanthal folds or hypertelorism) are minor physical features, the majority of cases remain undiagnosed. Tall stature is common, and especially the underarms and legs are longer. The girls may have their growth spurt earlier than controls. Clinically speaking, decreased head circumference is probably the most important common feature (Patwardhan et al., 2002; Ratcliffe et al., 1994). Motor and coordination abilities seem to be somewhat retarded, and the girls are sometimes described as being clumsy (Otter et al., 2010).

Since 1959 many physical disorders associated with TXS have been reported, most of which do not exceeding the population prevalence numbers. But there are some disorders that seem to be more common in TXS: urogenital anomalies, (partial) epilepsy and Premature Ovarian Failure (POF) and infertility (Tartaglia et al., 2010). A recent Danish database study using clinical diagnoses

and medication use in women with TXS, mosaics and controls revealed additional physical comorbidities, like gastrointestinal symptoms, including gastroesophageal reflux, constipation, and abdominal pain; dental problems; and increased risk of thrombophilia, venous thrombosis, and pulmonary embolism (Berglund et al., 2022).

Behavioural and psychiatric characteristics

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

There seems to be a higher prevalence of psychiatric illness in general in TXS (van Rijn, 2019). A study from Germany demonstrated that the extra X chromosome may influence mental health and well-being from childhood into adulthood. This study made clear that about half of the women TXS do not experience major mental health problems (Freilinger et al. 2018). This was confirmed by a recent study in a larger group of adults with TXS (Otter, Campforts, Stumpel, van Amelsvoort, & Drukker, 2022). This study showed a higher prevalence of major depressive episodes (43.3%, psychotic disorders (29.4%), suicidality (23.5%) and higher levels of anxiety. Impaired social functioning was found to be an important risk factor for psychotic disorders, affective disorders, trait anxiety, and low self-esteem (Otter, Campforts, Stumpel, van Amelsvoort, & Drukker, 2022). This Dutch study revealed no differences between women with TXS and controls in psychiatric medication use, which contrasts with the results of a Danish study, which revealed slightly higher levels psychiatric medication use, especially antipsychotics and medication used for ADHD (Berglund et al., 2022).

Scientific progress through neuroimaging findings

Neuroimaging findings in girls with an extra X chromosome demonstrated affected brain regions and related phenotypic characteristics such as language delay (thinner cortex was found in the lateral temporal lobes related to language functions), poor executive function and heightened anxiety (increased thickness in the medial temporal lobe in the vicinity of the amygdala, a region important for social cognition and linked to anxiety) through differences in cortical thickness (Lenroot et al., 2014). Poor executive function and frontal lobe abnormalities have been suggested to be related (van Rijn & Swaab, 2015).

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

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Data on intelligence in girls and adolescents are consistent, indicating that the full-scale IQ is almost 20 points lower in these girls than expected in the family (Robinson et al., 1990). Whether the girls show problems in reading or arithmetic is not uniformly reported in the case reports. Clinical experience suggests that some difficulties during arithmetic lessons result from language disorders. Mild or serious academic problems/special educational needs are common (Bishop et al., 2011; Robinson et al., 1990). Further research is needed to confirm the findings on the increased prevalence of attention problems and explain these attention problems: are they due to receptive language disorder, auditory processing disorders, anxiety disorders or attention deficit disorder (ADD) (Lenroot et al., 2014)? Clinical experience treating ADD with medication suggests that the treatment is less effective than in 46,XX cases; however, controlled treatment studies are lacking (Leggett et al., 2010). A recent study in adults revealed that women with TXS score lower in general intellectual functioning and have impairments in motor processing speed and attention compared to controls, but do not differ with respect to executive functioning (Otter, Campforts, Stumpel, van Amelsvoort, Vingerhoets, et al., 2022). Women with TXS performed worse on an Emotion Recognition Task, particularly concerning recognising sadness, fear and disgust, so-called negative emotions (Otter et al., 2021).

Available guidelines for behavioural assessment/ treatment/management

There is no evidence-based management guideline, although Otter et al. have proposed a guideline of medical and behavioural/psychiatric assessment (Otter et al., 2010). It is our advice to use a broad set of tools when psychological complaints are present since recent studies indicate language impairments in children (Bishop et al., 2018; Capelli et al., 2022), social-behavioural problems in children (Wilson et al., 2019) and adults (Otter et al., 2021), and neurocognitive problems in children (Urbanus et al., 2020) and adults (Otter, Campforts, Stumpel, van Amelsvoort, Vingerhoets, et al., 2022). A psychiatric interview should be included in a careful examination of children (van Rijn, 2019) and adults (Otter, Campforts, Stumpel, van Amelsvoort, & Drukker, 2022).

Useful websites/associations for more information

- The Dutch parents' support website: http://triple-x-syndroom.nl/. This website shows many links to scientific papers and useful links, e.g., links to international chat pages for parents and TXS girls/women. Scientific papers and syndrome sheets are available in several languages: English, French, Spanish, German and Dutch.
- Unique, a parents support group from the United Kingdom provides a syndrome sheet with information on physical and behavioural developmental issues: https://www.rarechromo.org/media/information/Chromosome_X/Triple_X_syndrome%20Trisomy_X%20FTNW.pdf ; https://rarechromo.org/media/information/Chromosome_X/Disclosing_about_XXX_for_girls%20FTNW.pdf ; https://rarechromo.org/media/information/Chromosome_X/Disclosing_about_XXX_for_parents%20FTNW.pdf and https://rarechromo.org/media/information/Chromosome_X/X%20inactivation%20QFN.pdf .
- The AXYS website provides a lot of information: https://genetic.org/variations/about-trisomy-x/. Especially parents and TXS girls/women in the United States will find opportunities to meet experts, other parents and TXS girls/women. AXYS is active in fundraising for the support of scientific research.

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Tuberous Sclerosis Complex (TSC)

First description and alternative names

Even though earlier cases exist, the first detailed description of the disorder was by Désiré-Magloire Bourneville, a French Physician, in 1880 when he described the case of a young girl with severe intractable epilepsy, intellectual disability and a 'confluent vesiculo-papular eruption on her nose, cheeks and forehead'. Neuropathology showed white, potato-like growths in the brain, referred to by Bourneville as 'tuberous sclerosis of the cerebral convolutions'. The term tuberous sclerosis *complex* was introduced by Moolten in 1942 to describe the multi-system nature of the disorder. The abbreviation 'TSC' is used (Curatolo, Moavero & de Vries, 2015).

Genetics and Molecular Biology

Occurs as a spontaneous mutation in 70% of cases. Autosomal dominantly inherited in the remaining 30% of familial cases. The disorder is associated with mutations in one of two genes, *TSC1* (on 9q34) or *TSC2* (on 16p13.3). The TSC1 and TSC2 proteins form an intracellular complex that links a number of intracellular signalling pathways including the AMPK pathway, the MAPK pathway and the PI3K pathway. The TSC1-2 complex functions upstream of mTOR (mammalian/ mechanistic Target Of Rapamycin). TSC mutations cause mTOR overactivation, leading to dysregulation of cell growth, proliferation and various other fundamental neurobiological processes. mTOR inhibitors have been approved by the FDA and EMA for the treatment of brain SEGA (subependymal giant cell astrocytoma), renal angiomyolipoma, and treatment-resistant epilepsy associated with TSC. Topical preparations of mTOR inhibitors are frequently used for facial angiofibromas and other skin manifestations of TSC. Clinical trials of mTOR inhibitors are underway for neuropsychiatric features of TSC, but have so far shown mixed results, at least in part due to the highly heterogeneous nature of the behavioural phenotype of TSC (see Curatolo, Moavero & de Vries, 2015 for primary references).

Incidence/prevalence

Birth incidence of about 1 in 5,800 (Osborne et al., 1991, see Curatolo, Moavero & de Vries, 2015 for primary references).

Physical features and natural history

Wide variability of expression. The previously used "diagnostic triad" (of epilepsy, intellectual disability and characteristic facial skin lesions) is seen in only about 30% of people with the disorder. TSC is multi-system and can include hamartomatous growths affecting the brain, skin, kidneys, heart, eyes, teeth, lungs and other organs. About 70-80% of people with TSC have a lifetime history of epilepsy. Diagnosis is based on meeting clinical criteria for the disorder or having a pathogenic mutation in one of the TSC genes (Northrup et al., 2021). Mutations are identified in >90% of individuals with clinically confirmed TSC and mosaic mutations in a further proportion.

TSC is not an inevitably declining condition, and any deterioration in physical or neuropsychiatric profile should be further investigated. Life expectancy is influenced by the degree of physical and neurological involvement. Intractable seizures, SEGA and renal failure secondary to angiomyolipomas may be causes of death. However, molecularly-targeted treatments with mTOR inhibitors are now available for many of these manifestations (see Curatolo, Moavero & de Vries; de Vries, Wilde et al., 2018 for primary references).

Behavioural and psychiatric characteristics

Tuberous Sclerosis is associated with a wide range of behavioural, psychiatric, intellectual, academic, neuropsychological and psychosocial difficulties. The term 'TAND' (TSC-Associated Neuropsychiatric Disorders) was coined in 2012 as an umbrella term for all the bio-psycho-social aspects of the disorder (de Vries et al., 2015) and a TAND Checklist has been developed to aid clinical teams to screen for TAND (de Vries et al., 2015; Leclezio et al., 2015). In 2023 a self-report, quantified TAND Checklist (TAND-SQ) was published (Heunis et al., 2023). At the behavioural level, TSC is associated with high rates of mood/anxiety, overactive/impulsive, sleep/eating, dysregulated behaviours (aggression and tantrums), and many autism-related behaviours. At the psychiatric level, neurodevelopmental disorders are common, with autism spectrum disorders (ASD) in 40-50%, ADHD and attention-related disorders in 30-50% and intellectual

disability in ~50% of individuals. TSC is one of the medical conditions most commonly associated with ASD. In adolescents and adults, very high rates of anxiety and mood disorders are reported. Psychotic disorders should raise the possibility of seizure-related psychopathology (de Vries et al., 2015).

Neuropsychological characteristics

At the intellectual level, more than 50% of individuals with TSC will have global intellectual abilities in the normal range, but often with an uneven profile of strengths and weaknesses. Intellectual abilities tended to show a bimodal distribution in TSC where 30% of individuals with TSC had profound global intellectual disability (IQ equivalent <20) and the remaining 70% fell on a normal distribution curve, shifted to the left. Interestingly, the bimodal distribution of IQ has become less pronounced in TSC research studies over the last decade. At the scholastic/academic level, almost 60% of people with TSC will have a history of reading, writing, spelling or mathematics difficulties (de Vries et al., 2018; de Vries, Wilde et al., 2018). At the neuropsychological level, there are high rates of specific neuropsychological deficits, even in those with normal or high global intellectual abilities. Specific deficits are most prominent in attentional, executive and visuo-spatial skills. These neuropsychological deficits may be associated with significant impairment of functional abilities in daily life (de Vries, Wilde et al., 2018; Curatolo, Moavero & de Vries, 2015; de Vries et al., 2015).

Available guidelines for behavioural assessment/ treatment/management

- International consensus guidelines were drawn up for the assessment of cognitive and behavioural problems in TSC (de Vries et al., 2005). These were revised and are augmented by the new guidelines on screening and assessment (Krueger, Northrup et al., 2013) and by the TAND Checklist (de Vries et al., 2015; Leclezio et al., 2015). The most recent update of diagnostic criteria and treatment guidelines were published in 2021 (Northrup et al., 2021).
- There are currently no TSC-specific treatments available for the neuropsychiatric manifestations of TSC. Clinicians should therefore use evidence-based interventions as for the general population. International consensus recommendations for the identification and treatment of TAND is expected in 2023.
- Targeted treatments using mTOR inhibitors are currently in clinical trials for TSC-associated neuropsychiatric disorders (TAND) (Curatolo, Moavero & de Vries, 2015; de Vries, Wilde, et al., 2018), but these are not at present recommended outside clinical trials.

Useful websites/associations for more information

- www.tuberous-sclerosis.org
  [UK user/carer organization]
- www.tsalliance.org
  [USA user/carer organization]
- www.tscinternational.org
  [International user/carer organization]
- www.tscinternational.org
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Petrus J de Vries & Anna Jansen, Updated July 2023

Turner syndrome

First description

Henry Turner first described Turner syndrome in 1938, but it was not until 20 years later that the genetic basis of the syndrome was discovered. About 50% of clinically identified cases of Turner syndrome are associated with a single X chromosome (X-monosomy, XO), and affected females therefore have 45 rather than the usual 46 intact chromosomes.

Genetics and molecular biology

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

Incidence and prevalence

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

Physical features and natural history

There are many possible physical characteristics of the syndrome, but none is invariable. If the condition is not detected at birth (usually suspected because of a transient edema maximal over the lower legs and feet, which rapidly clears) the diagnosis may not be made until middle childhood. The usual reason for ascertainment is growth delay.

Specific characteristics include a narrow, high-arched palate, which is associated with severe feeding difficulties in infancy. These are not only due to the palatal problem but also to oromotor immaturity. There are low-set ears, a low hairline, and occasionally a webbed neck (this latter feature being much rarer than textbook descriptions would suggest). The eyes may show strabismus and a slight ptosis. The chest is typically broad, with widely spaced breasts. When standing with her arms at her side, the lower arms typically turn out at the elbows (described as a wide carrying angle).

Some form of cardiac abnormality occurs in approximately one-third of Turners patients. Problems are primarily left-sided and may include coarctation of the aorta and bicuspid aortic valve. Individuals with Turner syndrome are also at higher risk for hypertension and should receive an echocardiogram or MRI to evaluate the heart at the time of diagnosis regardless of age.

Other common problems include renal anomalies (30%) associated with an increased risk of urinary tract infections and hypertension. Hypothyroidism is associated with an autoimmune thyroiditis. One of the most serious, but often overlooked, complications is recurrent otitis media, exacerbated by anatomical anomalies of the Eustachian tube. This is extremely common, and occurs in up to 80%. The onset is later than in typical children, between 4-15 years of age. Aggressive treatment of infections is appropriate. The majority (50-90%) of women with Turner syndrome will also develop early sensorineural (nerve) hearing loss, with gradual deterioration from childhood. They may require hearing aids earlier than the general population.

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Because of the small stature, which is almost invariable relative to the height of the parents, it has become usual to treat with human growth hormone. The average stature after treatment is increased by a few centimeters, although the condition is not associated with growth hormone insufficiency and high doses are needed to achieve any significant benefit. There is no evidence that treatment with growth hormone benefits psychosocial adjustment, although it may improve self-esteem.

Behavioural and psychiatric characteristics

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

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

Neuropsychological characteristics

Almost all have normal verbal intelligence. About 80% have relatively poor visuospatial memory (approx. 1 SD below norms), and this can have practical consequences, such as a tendency to lose one's way in unfamiliar environments. Some motor skills may be impaired; clumsiness is typical, especially in fine motor tasks. Very poor arithmetical abilities, found in the majority, reflect slow processing speeds and a fundamental conceptual problem with numerical magnitude.

Socio-perceptual processing is impaired to some extent in at least one third, with difficulties remembering faces or differentiating facial expressions of emotion. Socio-cognitive anomalies in Turner syndrome extend to deficits in mentalizing abilities. In common with females who have idiopathic ASD, girls with Turner syndrome attempt to compensate for their social deficits from early childhood. They develop superficially good and engaging social skills, which are learned from imitation, but may become associated with social disinhibition. Poor attention is typical during early and middle childhood, leading to the appearance of attention deficit hyperactivity disorder. This often resolves by adolescence.

Available guidelines for behavioural assessment/ treatment/management

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- Gravholt C.H.(2009) *"Turner – know your body!"* Editor –Published by Novo-Nordisk. Available as a free web-publication http://np.netpublicator.com/netpublication/n75088268

Useful websites/Associations for more information

- Turner syndrome support society (UK): http://www.tss.org.uk/
- National Institute of Child Health and Human Development (USA): http://turners.nichd.nih.gov/

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David H Skuse, 2014

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

First descriptions and alternative names

As is so often the case, chromosome **22q11.2 deletion syndrome (22q11.2DS)** was first described independently by several perceptive clinicians back in the 1950s to 1970s. As these clinicians were experts within different specialties and therefore not focussing on the same medical problems, several constellations of features were described as separate conditions. The first person to describe children who most likely had 22q11.2DS was the otolaryngologist (i.e. ear nose and throat specialist) Eva Sedlačková who already in 1955 described children with hypernasal speech associated with a congenitally shortened soft palate, facial dysmorphology and intellectual impairments [1-4]. She was later to show that many of these children also had cardiac malformations and submucous clefts. Following Sedlačková's observations, other clinicians such as the endocrinologist Angelo DiGeorge (first English publication) described children with presentations of immunodeficiency, hypoparathyroidism and congenital heart disease [5], the physician Kinouchi described children with cardiac abnormalities and a typical face [6] and the speech-language pathologist Robert Shprintzen described children with cleft palate, cardiac anomalies, a typical face and learning problems [7]. To avoid confusion, the syndrome is nowadays typically referred to as 22q11.2 deletion syndrome, a description based on its underlying genetic cause, however **alternative names for the syndrome are velo-cardio-facial syndrome (VCFS), velofacial hypoplasia, Sedlačková syndrome, DiGeorge syndrome, Shprintzen syndrome, Cayler syndrome, conotruncal anomaly face syndrome and cardiac defects, abnormal facial features, thymic hypoplasia, cleft palate, and hypocalcemia (CATCH 22)**.

Genetics/aetiology

Whilst visible cytogenetic deletions were identified in about one quarter of children with DiGeorge syndrome in the mid-1980s, it was not until the early 1990s that the microdeletions of chromosome 22q11.2 was identified as the cause of most cases of DiGeorge syndrome and that indeed, children with other groupings of symptoms, including most of those with VCFS, were found to share the genetic aetiology [8, 9]. Whilst the microdeletions vary in size, the deletion typically encompasses 0.7 to 3 million base pairs, a region that contains approximately 50 genes. The majority of people diagnosed with 22q11.2DS have a de novo or spontaneously occurring deletion and a smaller proportion (about 15%) have an inherited deletion. The deletion is inherited in an autosomal dominant manner, meaning that if a person has the deletion there is a 50% chance that the deletion will be passed on to their offspring.

Incidence/prevalence

Generally the prevalence of the syndrome is described to be 1 in in 2148 live births and 1 in 992 pregnancies [10, 11]. However, it has been argued that the syndrome is still clinically under-recognised with many older individuals diagnosed when they themselves have children diagnosed with the syndrome [12, 13]. Whilst most people, including many health care professionals, have not heard of 22q11.2DS it is the most common cause of syndromic palatal anomalies and also one of the most common causes of congenital heart defects and developmental delay [13]. It is also likely that the prevalence of the syndrome will rise as mortality decreases and reproductive fitness increases [14, 15]. The syndrome affects individuals of both sexes and of different ethnic background equally [16] although it has been suggested that there are sex differences in the expression of the syndrome [e.g., 17, 18].

Physical characteristics

22q11.2DS is a multisystem disorder including more than 180 characteristics. However, there is a large variability in the expression of the phenotype even amongst members of the same family and characteristics can range from life threatening to very mild [19]. The most common features include congenital heart defects (including conotruncal anomalies), thymic hypoplasia/aplasia, palatal anomalies (including submucous cleft palate and/or velopharyngeal incompetence); immunodeficiency;

hypocalcaemia; vascular anomalies; feeding difficulties; gastrointestinal issues; scoliosis; sleep disorders; hypotonia and subtle, but characteristic, facial features [9, 13, 20]. Due to the multisystemetic impact of 22q11.2DS, it is important that each individual has an individualised care plan involving a multidisiplinary health care team.

Cognitive characteristics

Whilst there is a large variability within the cognitive profile of individuals with the syndrome, cognitive impairments are very common and are associated with learning problems. Intellectual functioning typically range from low average to mild intellectual disability with the majority of individuals having an intellectual ability in the borderline range [21]. Typically, verbal intellectual functioning decline slightly with increased age but more so in the presence of psychosis [22]. Specific cognitive impairments in executive functioning, memory, working memory, sustained attention, visual-spatial processing are common [e.g., 23, 24]. In addition, individuals with the syndrome have been found to have deficits in social cognition including problems in interpreting facial expressions, theory of mind and social perception [e.g., 25, 26-28]. Problems with understanding maths are common in 22q11.2DS and specific learning disorders including mathematics (dyscalculia) are often diagnosed with significant impact on daily living skills [29].

Behavioural characteristics

Emotion dysregulation is a commonly occuring difficulty for people with the syndrome. There has been reports that children and adults experience both internalising and externalising behaviours with early reports suggestive of extremes of behaviour including temper outbursts as well as shyness and withdrawal [30]. A recent paper found that while some people with 22q11.2DS have not difficulties with emotion regulation, other people may predominantly have either internalising or externalising problems or a combination of the latter [31]. Overall, it was found that externalising problems including aggression is associated with having more difficulties in everyday life. People with 22q11.2DS who also have emotion regulation difficulties are more likely to have diagnoses of autism, attention deficit hyperactivity disorder, anxiety or depression [32, 33]. Adults who also have a diagnosis of schizophrenia are also at an increased risk of aggressive behaviours [34, 35].

Social relationships can be problematic for people with 22q11.2DS, there has been reports of difficulties with social skills and social-cognition that may make it more difficult to initiate and maintain friendships as well as understanding social dynamics [36]. This may be further complicated by emotion dysregulation and more general cognitive difficulties. There has also been reports that many people with the syndrome are victimised or bullied at school with clear impacts on mental health and wellbeing [37].

Mental Health and Wellbeing

Children with 22q11.2DS are at higher risk of being diagnosed with psychiatric disorders such as attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder, anxiety disorders (generalised anxiety disorder, separation anxiety, and phobias) and autism [38]. It has been proposed that as many as 60-70% of children with 22q11.2 have at least one diagnosed psychiatric disorder. In late teenage years and early adulthood there is an increased risk of depressive disorders and also a high risk of psychotic disorders including schizophrenia. Low full-scale IQ (FSIQ) in childhood, early cognitive decline, and inattentive symptoms have been found to be risk factors for the development of psychotic symptoms [22, 39]. However, conduct disorder and substance use disorder diagnoses are rare in the syndrome. Most of the psychiatric disorders persist into adulthood [20]. Many people with the syndrome have more than one psychiatric diagnosis, highlighting the complexity of care [38]. There are indications in the literature that despite the high prevalence of psychiatric disorders, many individuals with 22q11.2DS are not receiving the appropriate psychiatric care [40]. It is also important to note that psychiatric symptoms are likely to be impacted by sleep disorders and fatigue that are common in the syndrome and that has a significant impact on quality of life [41-44].

Family functioning

Parents of children with 22q11.2DS report higher levels of parenting stress and poorer mental health compared to parents of typically developing children [45, 46]. Parents often struggle with managing concerns related to their child's diagnostic journey, interactions with the health care system, education and mental health [47, 48]. The concerns of parents often change over time with an initial focus on the health care needs and speech issues of children in early childhood, changing to a focus on intellectual, learning, social and anxiety related issues in mid-childhood. Around this age there are also increasing concerns about independence and mental health [49]. There has been suggestions that, as in other similar conditions, there is an association between parental stress and mental health and child outcomes [45, 46, 50]. It is important to remember that in order to look after a person with 22q11.2DS well, it is important to consider the whole family system [48].

Available clinical guidelines

- Updated clinical practice recommendations for managing children with 22q11. 2 deletion syndrome
- Updated clinical practice recommendations for managing adults with 22q11.2 deletion syndrome

Useful websites/associations for more information

- International 22q11.2 Foundation
  http://www.22q.org/
- 22q11.2 Society
  http://www.22qsociety.org/
- 22q Foundation Australia and New Zealand
  https://www.22q.org.au/

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Linda Campbell : July 2023

Williams Syndrome (also known as Williams-Beuren Syndrome)

First descriptions:
The syndrome was first described by Williams *et al.* (1961) in four patients with supravalvular aortic stenosis (SVAS) in association with intellectual disability and an unusual facial appearance, and by Beuren *et al.*(1964). Black and Carter (1963) associated this characteristic facial appearance with that found in idiopathic infantile hypercalcaemia, a name initially used for the syndrome.

Genetic aspects:
Williams syndrome is a genetically determined neurodevelopmental disorder caused by a heterozygous deletion of about 1.6 Mb (approx. 26 – 28 genes) on chromosome 7 (7q11.23). A deletion of the elastin gene (ELN) which occurs in >99% of individuals with WS) is associated with congenital heart disease and connective tissue abnormalities including hernias and premature ageing of the skin. Several genes are also implicated in the intellectual disabilities and cognitive deficits observed in WS, including GTF2I, LIMK1 and CYLN2 (see Kozel *et al*., 2021; Morris, 2017; Morris & Mervis, 2021, 2017 for reviews). Transmission is autosomal dominant and although most cases are de novo occurrences, some instances of parent to child transmission have been reported (Donnai & Karmiloff-Smith, 2000).

Incidence:
The condition is estimated to occur in 1 per 20,000 individuals although higher rates (1 in 7500) have been reported (Kozel *et al*., 2021).

Physical phenotype and natural history:
The condition typically presents in infancy with difficulties in feeding, irritability, constipation and failure to thrive. The physical phenotype is remarkably consistent across the world (Kruszka *et al*., 2018) and the principal characteristics are well summarised by Kozel *et al*., (2021). The main features include: endocrine and growth abnormalities (pre-natal growth deficiency, failure to thrive in infancy, infantile hypercalcaemia, hypercalciuria, hypothyroidism, early puberty); cardiovascular disease (mainly 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 (Kozel *et al*., 2021) but verbal IQ is typically higher than non-verbal IQ and there are complex, and often subtle, pattern of peaks and valleys within each of these domains. Research into the nonverbal abilities of individuals with WS has highlighted particular deficits in domains such as number skills, planning, problem solving and spatial cognition. In contrast, face processing and some aspects of social cognition tend to be relative strengths. Within the verbal domain, auditory rote memory and receptive vocabulary are viewed as strengths, while spatial language (e.g. using spatial terminology), expressive vocabulary, syntax, semantics and grammatical comprehension are generally delayed (see Royston *et al*., 2019 for review); pragmatic language difficulties may also become more apparent with age (Van Den Heuvel *et al*., 2016). Adaptive behaviour skills are often relatively poor (Fu *et al*., 2015; Howlin *et al*., 2010) but research findings

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on the association between IQ and adaptive behaviour are inconsistent. Profiles of adaptive functioning also vary with age although Social/Communication skills tend to be more advanced than Daily Living Skills, especially in children and adolescents (Brawn and Porter, 2018).

Individuals with WS tend to show particular patterns of emotional and behavioural difficulties (Einfeld *et al.*, 2001;Morris, 2017). An intense drive for social interaction is one of the most characteristic traits and is evident from early childhood (Riby *et al.*, 2017). However, older children and adults with WS have difficulties making and sustaining friendships and because of their desire to make social contact they have a high risk of being bullied, exploited or abused (Fisher *et al.*, 2017; Fisher & Morin, 2017). Other difficulties include hyperacusis, attentional problems, impulsivity, and externalizing (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)

Further information

- www.williams-syndrome.org.uk

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Wolf-Hirschhorn syndrome

Wolf-Hirschhorn syndrome (WHS) is a multiple congenital malformation syndrome first described in 1965 independently by Cooper and Hirschhorn and by Wolf, which presents with a broad range of clinical manifestations. It is caused by a partial loss of genetic material at the telomere of the short arm of chromosome 4 and, specifically, from a deletion of the terminal 2 Mb of the 4p16.3 region (Figure 1) although the hemizygosity can be variable in size and ethiology. The high variability present at both clinical and molecular level can cause difficulties in diagnosis of WHS.

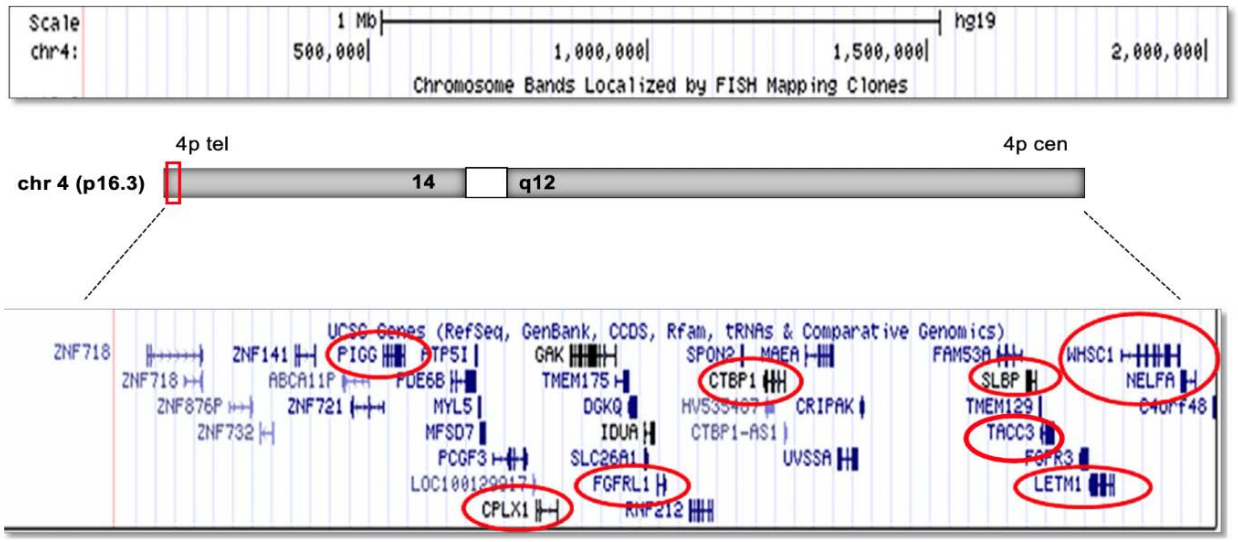

Figure 1. Diagram showing the distal region of chromosome 4p, where candidate genes for seizures and craniofacial features map (LEMT1 and WHSC1; Zollino *et al.*, 2003; Rodrıguez *et al.*, 2005). [Diagram was modified from Battaglia *et al.*, 2015].

Genetics and Molecular Biology

The genotype often arises from an unbalanced translocation event (t4;8) (p16;23). Most often, however, the genotype is produced by a de novo mutation. The mechanism(s) which produce the deletion are not known, but recent studies suggest that genes within sub-telomeric regions are likely to be involved in deleterious chromosomal rearrangements. Deletion size in WHS varies; it is most often telomeric, but it can also be interstitial. It is usually detected by conventional karyotyping or fluorescence in situ hybridization (FISH) (50-60%). de novo microdeletions account for approximately 25–30% and, unbalanced translocations (de novo or inherited) and complex genomic rearrangements, as ring 4 chromosome, are observed in approximately 15% if the cases (Battaglia *et al.*, 2001; 2009; Lurie *et al.*, 1980). However, it has been suggested that the prevalence of unbalanced translocations leading to WHS is underestimated as they could be missed by karyotyping and FISH (South *et al.*, 2008). Submicroscopic deletions are also observed in WHS and often identified by multiplex ligation-dependant probe amplification (MLPA) and/or by CGH arrays (Ho *et al.*, 2016; Wright *et al.*, 1997). The size of the deletion has been associated with the severity in the phenotype and results, in part, to the wide variability of the clinical presentation. For a complete WHS diagnosis in the proband, chromosomal analysis is recommended also for the parents, in order to establish the risk of recurrence of other family members.

Twelve genes identified by the human genome project between 1.2 and 2.0Mb from the telomere of 4p, five (WHSC1, WHSC2, TACC3, SLBP and HSPX153) are suspected of encoding proteins involved in mRNA processes or transcription.

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Recent exome sequencing analyses led to the identification of two genes within the (WHSCR): the WHS candidate gene 1 (WHSC1), also known as nuclear receptor-binding Set Domain-protein 2 (NSD2), contained only partly within the WHSCR (Derar *et al.* 2019), and WHS candidate gene 2 (WHSC2), also known as Negative Elongation Factor Complex Member A (NELFA), entirely contained within the WHSCR (Cyr *et al.* 2011). Specifically, two minimal critical regions, have been identified corresponding to the smallest region, whose haploinsufficiency leads to the core WHS phenotype (Rauch *et al.* 2001; Zollino *et al.* 2003; Rodriguez *et al.* 2005). Furthermore, WHSC1 and SLBP genes, are both involved in histone metabolism, and therefore might affect the expression of other genes. Hence, it is likely that some of WHS pathology results from the combined effects of haploinsufficiency in more than one of these genes and generating significant biological changes in the expression of the correspondent target genes.

Prevalence and Mortality

The genotype is relatively rare – estimates of its prevalence range from 1:20,000-50,000 live births with a 2:1 female-to-male ratio (Maas *et al.*, 2008). Mortality rate in the first two years of life is high [~21%]. However, the median life expectancy for those who survive is greater than age thirty years. Nonetheless, life expectancies are far greater for other microdeletion cases than for WHS..

Physical, Behavioral and Neuropsychological Features

Clinical characteristics of the phenotype include growth delay, hypotonia, unusual idiosyncratic distinctive craniofacial appearance - "Greek warrior helmet" – that are the combined result of microcephaly, broad forehead, prominent glabella, hypertelorism, high arched eyebrows, short philtrum and micrognathia. In addition, are variable observed clinical manifestations severe feeding difficulties, and congenital anomalies like skeletal anomalies, heart lesions, oral facial clefts, senso-neural deafness, and genitourinary tract defects (Battaglia *et al.* 2001).

Most individuals with WHS are prone to seizures, have mild to profound intellectual disability, attention deficits and limited, if any, expressive speech, and language. Children with WHS are more severely impacted (~ 65% are profoundly ID) in both general cognitive ability and overall adaptive behavior skills compared to children with other microdeletions. Among less severely affected children, i.e., those who have expressive language, the profile of mean cognitive abilities and deficits is relatively flat and extends to all cognitive areas tested: verbal, quantitative, and abstract/visual reasoning, and short-term memory. Interestingly, and despite their limitations in cognitive ability and overall adaptive behavior, children with WHS exhibit relative competence in socialization skills compared to their abilities in other adaptive behavior domains (Fisch *et al.* 2010). On the other hand, they often have significant social problems, as assessed by the Conners Parent Rating Scale and Child Behavior Checklist. Limited attention span among children with WHS likely has a negative impact on their short-term memory skills. To that extent, these difficulties are not unique to the WHS phenotype. The proportion of children with WHS with autism or autistic-like features is significantly lower than the rates of autism found in the other sub-telomeric disorders such as 2q37, 8p23 and 11q22-25 (Jacobsen syndrome).

Although the variability in the broad range clinical manifestations observed in WHS, can be in part explained by the extent of the deletion, it is more likely that a synergistic effect of the haploinsufficiency of the genes mapping within the deleted area and additional factors including genetic backgrounds, allelic variation in the non-deleted regions of the other chromosome 4 and unbalanced translocation (Zollino *et al.* 2000; South *et al.*, 2008) lead to the observed heterogeneous phenotype.

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Gene Fisch 2014. Updated in 2022 by Flora Tassone

47,XYY Syndrome

First description and molecular biology

47,XYY; XYY syndrome; YY Syndrome; Jacob's syndrome. The first case of XYY syndrome was reported as an incidental finding by Adam Sandberg and colleagues in 1961. Four years later, Patricia Jacobs, a British geneticist, further researched this chromosome aneuploidy and described it in great detail; thus, the presence of an extra Y chromosome is also called Jacob's syndrome.

Genetics and molecular biology

The majority of cases of XYY syndrome are due to a paternal non-disjunction during meiosis II, following a normal meiosis I; a few cases resulting in an additional Y chromosome. In some cases, it arises during early embryogenesis in a post-zygotic mitotic error, in which case it can result in a 46,XY/47,XYY mosaic form (Robinson & Jacobs, 1999).

Incidence/prevalence

The prevalence of 47,XYY is currently estimated at approximately 1:1000 males. Since 47,XYY is typically not associated with marked phenotypic characteristics, it remains frequently under-detected with 90% of cases never diagnosed in their lifetime (Abramsky & Chapple, 1997). Of those diagnosed, most cases are diagnosed postnatally and late in life. However, 47,XYY may be increasingly detected prenatally through non-invasive prenatal screening (NIPS). This screening should be confirmed prenatally (amniocentesis or chorionic villus sampling) or postnatally (chromosome karyotype analysis performed by a blood sample or by a chromosomal microarray). A chromosomal microarray (CMA) test can consist of an oral cheek (buccal) swab or blood test. A cheek swab is an easy and painless way to detect abnormalities of chromosome numbers to provide a definitive diagnosis.

Physical features and natural history

Physical phenotypic differences associated with XYY syndrome are usually mild. Hypertelorism,(small h) macrodontia, pes planus, central adiposity, clinodactyly, larger head circumference than typically developing boys have been described (Bardsley *et al.*, 2013; Lalatta *et al.*, 2012). Speech delay is common. Delayed development of motor skills (such as sitting and walking), weak muscle tone (hypotonia), and behavioral and emotional difficulties are also frequent. Boys have increased growth velocity during childhood, and adult height is usually increased approximately 7cm (3") above what is expected (Aksglaede *et al.* 2008). 47,XYY men are usually taller than 1.85m or 6 ft 5 inches, and the tall stature can be explained by the presence of additional copies of the SHOX gene (and possibly also other genes related to stature). Cystic acne may develop during adolescence. Asthma prevalence is greater in XYY than in the general population (Bardsley *et al.*, 2013).

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

Behavioral and psychiatric characteristics

Individuals with XYY syndrome may be at increased risk for behavioral problems and psychiatric disorders. There is an increased rate of diagnosis of attention deficit hyperactivity disorder (ADHD) [more marked than in 47,XXY (KS)], and increased risk of problems with distractibility, impulsivity, difficulties with temper management. Problems with social relatedness are also common. Individuals with XYY have been reported as having increased scores on measures of autistic spectrum disorders (ASD) symptoms, however, previous studies have been confounded by many factors. Further investigation is necessary before a definitive answer can be given on the association of ASD and XYY.

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

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boys diagnosed postnatally and are often the reason these boys had karyotype evaluation (Bardsley *et al.*, 2013). Risk for psychosis may be increased in men with 47,XXY (Verri *et al.*, 2008).

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

Neuropsychological and neurological characteristics

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

Voxel-based morphology (VBM) revealed that boys with 47,XYY have altered GM volume in the insular and parietal regions relative to neurotypically developing boys (Lepage *et al.*, 2014). Alterations in gray matter volume may account for the reduced motor coordination typically seen in 47,XYY boys. VBM also found extensive WM modifications bilaterally in the frontal and superior parietal loves in 47,XYY boys (Lepage *et al.*, 2014). These white matter differences in the frontal and superior parietal lobes parallel a high prevalence of language-based learning difficulties (specifically dyslexia), spatial orientation deficits, and graphomotor dysfunction characterized in the 47,XYY profile.

White matter volumes are typically larger in the frontotemporal region of the brain, which allows for efficient brain signaling and coordination between visual memories, language comprehension, and emotional association systems. Insular and frontotemporal gray and white matter is reduced in males with XYY, specifically in known language areas (Bryant *et al.*, 2012). These patterns are distinctive and distinguishable from neuroanatomical patterns in typically developing boys and those with XXY. The patterns of regional gray matter and white matter variation in XYY boys are associated with deficits in motor and language abilities (Bryant *et al.*, 2012). These studies further link brain development, behavior, and developmental outcome in another XY chromosomal disorder and provide a possible mechanistic support that X and Y chromosomes may differentially impact brain morphology.

47,XYY syndrome is associated to higher risk for seizures, focal epilepsy, and an electroclinical pattern characterized by focal spike and waves (similar to benign focal epilepsy) has been described in 47,XYY boys (Torniero, 2010). Males with 47,XYY show increased total gray matter (GM) and white matter (WM) volume when compared to 46,XY and 47,XXY males (Bryant, 2012). Increased grey matter may be the result of reduced synaptic pruning, leading to altered synaptic function and perhaps increased seizure risk (Bardsley, 2013).

Available guidelines of behavioral assessment/ treatment/management

Once 47,XYY has been diagnosed, a comprehensive neurodevelopmental evaluation is important for the management of this syndrome (Samango-Sprouse & Gropman, 2016). Occupational and physical therapy may be recommended for infants and young boys who have low muscle tone (hypotonia), and speech therapy may be needed for boys who have speech delay. Speech therapy should focus on eliminating the underlying oral motor weakness and dysfunction through a sensorimotor approach. In the school setting, assistance from special educators or individualized education programs (IEPs) may benefit the child.

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

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Useful websites/associations for more information

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

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Notes

The 27th SSBP International Research Symposium

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