21st SSBP International Research Symposium

Translating knowledge of phenotype towards improved outcomes in neurodevelopmental disability

Programme Book

28th – 30th August 2018 • Melbourne, Australia

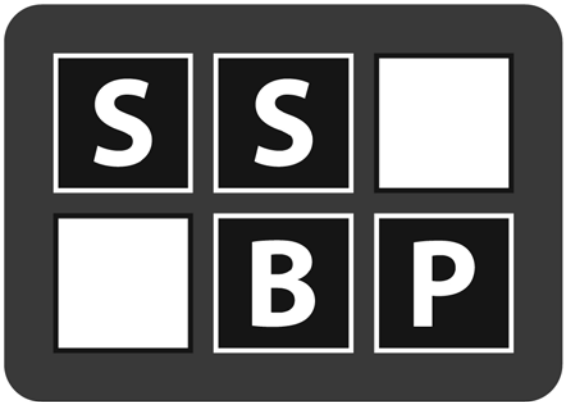
Save the date!

22nd SSBP International Research Symposium will be held in Birmingham, UK in September 2019

Registration and abstract submission open: 11th March 2019
Deadline for online abstract submission: 22nd April 2019
Deadline for discounted early bird registration: 26th July 2019
Educational Day: 4th September 2019
Research Symposium: 5th – 6th September 2019

Join us in Birmingham, UK for our 22nd Research symposium, the theme will be *Back to basics in behavioural phenotypes: insights from developing a detailed understanding of behaviour*

See **www.ssbpconference.org** 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

28th – 30th August 2018

The 21st SSBP International Research Symposium

Translating knowledge of phenotype towards improved outcomes in neurodevelopmental disability

Melbourne, Australia

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Welcome from the Conference Organisers

We are delighted to welcome you to Melbourne for the 21st SSBP International Research Symposium and Educational Day.

Melbourne has traditionally been a significant meeting place for the Wurundjeri, Boonerwrung, Taungurong, Djajawurrung, and Wathaurung people who together make up the Kulin Nation. Described on the following pages, we are pleased to have an Elder from the Wurundjeri People to welcome guests to Country at the start of our meeting. Europeans first visited the area that is now known as Melbourne in 1803, but it was not until 1835 that John Batman and John Fawkner began the first European settlement. The European settlement had a number of early names, including Bearbrass and Batmania, with the name Melbourne being selected in 1837 after the British Prime Minister William Lamb, Lord Melbourne.

The three days are filled by an exciting scientific program, which includes 15 plenary addresses as well as 19 presentations and 17 posters. We are looking forward to hearing about the latest behavioural phenotype research from the range of scholars, PhD candidates and students from 7 different countries. We hope that the range of presentations and disciplines will not only inspire engaging and interesting debate and discussion throughout the conference, but that this should also continue beyond your three days in Melbourne.

Today Melbourne is known for its rich multicultural heritage, beautiful parks and gardens, sport, and the arts. Take some time to explore some of the many restaurants, galleries and museums and laneways complete with street art. Sample the (world famous) Melbourne coffee, and perhaps even some of the local wines from the Yarra Valley and Mornington Peninsula.

We would like to thank the SSBP administration team and committee for all their help in the planning and preparation. Most of all, many thanks to you, the participants in this conference.

We hope you enjoy the conference and make some time to explore the beautiful city of Melbourne

Honey Heussler, Kylie Gray and Dawn Adams
Conference Coordinators

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Welcome to the land of the Wurundjeri people

© istockphoto

The Wurundjeri people are the Traditional Custodians of Melbourne and surrounding lands.

The Wurundjeri People take their name from the Woiwurrung language word '*wurun*' meaning the Manna Gum (*Eucalyptus viminalis*) which is common along '*Birrarung*' (Yarra River), and '*djeri*', the grub which is found in or near the tree. Wurundjeri are the 'Witchetty Grub People' and their Ancestors have lived on this land for millennia.

An Elder from the Wurundjeri People will formally welcome guests to Country.

Further information can be found at https://www.wurundjeri.com.au/

Melbourne Conference Organisers

A/Prof Honey Heussler

Dr Honey Heussler is a Developmental and Behavioural Paediatrician with dual Sleep Physician qualification. She is an Associate Professor with the University of Queensland and is Director of Developmental Paediatrics and Medical Director, Child Development Services as well as clinical responsibility in Behavioural and Sleep clinics with Children's Health Queensland

A/Prof Kylie Gray

Dr Kylie Gray is an Associate Professor and psychologist at the Monash University School of Clinical Sciences and Department of Psychiatry, and is the acting Director of the Monash University Centre for Developmental Psychiatry and Psychology. Her work has included addressing issues around diagnosis and assessment, development of assessment tools, mental health and psychosocial wellbeing of children and families, and the development and evaluation of supports and treatments. She is passionate about combining the disciplines of psychology, psychiatry and neuroscience to transfer clinically-driven research outcomes to the community and education systems in Australia and beyond.

Dr Dawn Adams

Dr Dawn Adams is a Senior Lecturer in the Autism Centre of Excellence Education at Griffith University, Brisbane, Australia. Her research interests focus upon the interaction between mental health and behaviour in individuals with neurodevelopmental disabilities, including autism and rare genetic syndromes. Her research also explores the impact of these behaviours on family members and those working with the young person in educational and community settings. Being a qualified Clinical Psychologist, Dawn is passionate about translating research into practice and regularly presents research findings to parent groups and clinicians in Australia and Europe.

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Scientific Committee

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

Dr Dawn Adams
Senior Lecturer,
Autism Centre of Excellence, Griffith University, Australia

Professor Anna Jansen
Head of Clinics,
Pediatric Neurology Unit, Department of Pediatrics, UZ Brussels, Belgium Neurogenetics Research Group and Mental Health and Wellbeing Research Group, Vrije Universiteit Brussel, Belgium

Professor Stewart Einfeld
Professor,
Brain & Mind Centre, The University of Sydney, Australia

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The SSBP

The **Society for the Study of Behavioural Phenotypes (SSBP)** is an international, interdisciplinary research society for studying the learning and behavioural problems of individuals with genetic disorders. 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

The SSBP Executive Committee

Life President	*Dr Martin* ***Bax*** (London)
President	*Professor Patricia* ***Howlin*** (UK) (patricia.howlin@kcl.ac.uk)
Chairman	*Prof Honey* ***Heussler*** *(Australia)* (h.heussler@health.qld.gov.au)
Hon. Secretary	*Professor Anna* ***Jansen*** (Belgium) (Anna.jansen@uzbrussel.be)
Hon. Treasurer	*Professor Andre* ***Strydom*** (UK) (a.strydom@ucl.ac.uk)
Committee	*Professor Stewart* ***Einfeld*** (Australia) (s.einfeld@usyd.edu.au)
	Professor Randi ***Hagerman*** (USA) (randi.hagerman@ucdmc.ucdavis.edu)
	Professor James ***Harris*** (USA) (jharrisd@jhmi.edu)
	Dr Stephan ***Huijbregts*** (the Netherlands) (shuijbregts@fsw.leidenuniv.nl)
	Professor Flora ***Tassone*** (USA) (ftassone@ucdavis.edu)
	D Jane ***Waite*** (UK) (j.waite@aston.ac.uk)
	Dr Kate ***Woodcock*** (UK) (K.A.Woodcock@bham.ac.uk)

Committee : International Representatives

Australia – *Stewart* ***Einfeld*** (Camperdown) (s.einfeld@usyd.edu.au)
USA (East Coast) – James ***Harris*** (Baltimore) (jharrisd@jhmi.edu)
USA (West Coast) – Randi ***Hagerman*** (Sacramento) (randi.hagerman@ucdmc.ucdavis.edu)
Global –*Pat* ***Howlin*** (London) (patricia.howlin@kcl.ac.uk)

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

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Meetings of the SSBP

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
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

Forthcoming Meetings of the SSBP

2019	Birmingham, UK	22nd International

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Tom Oppé and the Tom Oppé Distinguished Lecture

Tom Oppé

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

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

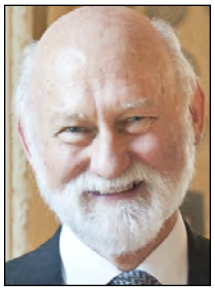
After some years at Great Ormond Street, a research fellowship at Harvard and 2 years in Bristol, he returned to St Mary's Hospital (where he had worked as Lecturer in Child Health), and stayed at St Mary's for the rest of his professional career. He was awarded a CBE in 1984 for services to paediatrics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

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

Tom Oppé Lecturers

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

2018 Tom Oppé Distinguished Lecturer: Emeritus Professor Bruce J. Tonge



MBBS, MD, DPM, MRC Psych, FRANZCP, Cert. Child Psych., RANZCP

Prior to his retirement in 2012 he was the Foundation Head, School of Psychology and Psychiatry and Head of the Discipline of Psychological Medicine at Monash University and also the Senior Clinical Advisor of the Mental Health Program of Monash Health at Monash Medical Centre in Melbourne, Australia. He has a distinguished record of clinical work, teaching and research in child psychiatry. He established the internationally recognised Monash University Centre for Developmental Psychiatry and Psychology. He continues to have clinical, research and teaching interests in the area of developmental psychiatry with a particular focus in the areas of Autism Spectrum Disorders and behavioural and emotional disturbance in children and adolescents with intellectual disability and neurodevelopmental disorders, parent education and skills training, public mental health interventions, and treatment outcome studies in childhood anxiety and depressive disorders.

Publications include: 13 books; 64 book chapters; 300 reviewed papers; 23 videos; 8 manuals and numerous invited addresses and competitive grant funding of $32M. He is editor of the *Handbook of Studies on Child Psychiatry* (Elsevier), co-author of the book *I just want you to be happy: preventing and tackling teenage depression* (Allen and Unwin), a co-author of *Autism: the early years* (Jessica Kingsley Press), author of the *Draw a Dream child mental state assessment technique*, and co-author of the *Developmental Behaviour Checklist*, an instrument which assesses behavioural and emotional problems in children and adolescents with intellectual disability. This instrument is widely used in clinical and research settings both in Australia and internationally.

He is the recipient of the Minister of Mental Health Victorian Public Healthcare Award for "Outstanding Individual Achievement in Mental Healthcare" in 2009, the RANZCP 2010 Meritorious Award for "Outstanding contribution to Psychiatry over many years", the 2010 ASPR Founder's Medal for "Contribution of significance to psychiatric research throughout career", the 2010 Monash University David de Kretser Medal for exceptional contribution to the Faculty of Medicine, Nursing and Health Sciences, and the Award for Distinguished Service to the Profession of Child and Adolescent Psychotherapists , VCPA, July 2011. He has served as Chair and board member of Autism Victoria, now AMAZE, and was the immediate past Chair and President and is now the Patron of the Mental Health Foundation Australia.

Patricia Howlin and the Patricia Howlin Prize Lecture

Patricia Howlin

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

Pat Howlin Prize Lecture:

Area of Research:

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

Eligibility of applicants:

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

Award Procedure:

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

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

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

Patricia Howlin Lecturers

2016	Shruti Garg
2015	Supriya Malik
2014	Hayley Crawford
2013	Mary Heald
2012	Sheena Grant
2011	Leah Bull
2010	Debbie Allen

2018 Pat Howlin Lecturer:

The Patricia Howlin Lecture Prize has not been awarded in 2018, 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 2019 conference.

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Venues

1 Research Symposium (28th - 29th August)

The Research Symposium will be held at:

State Library Victoria, Village Roadshow Theatrette
328 Swanston St, Melbourne, VIC 3000

(Entry from the LaTrobe St entrance)

Directions:
The State Library is opposite the Melbourne Central train station (in the city loop). Details of the Melbourne Metro network can be found at
www.metrotrains.com.au
Trams also stop outside the State Library.

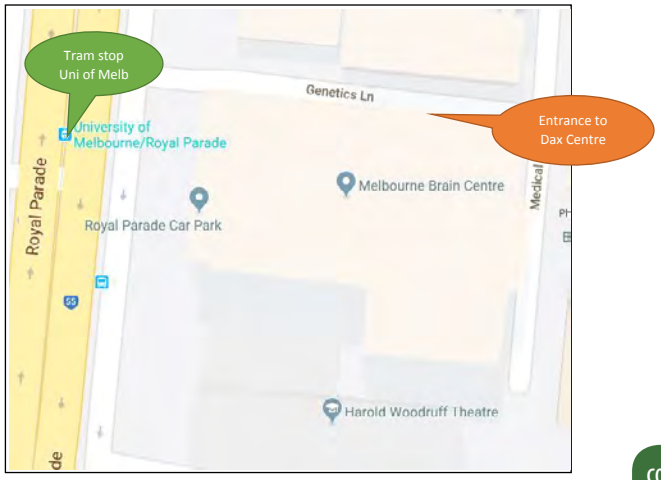
2 Conference Reception (28th August)

The Conference Reception will be held at:

The Dax Centre, Kenneth Myer Building,
30 Royal Parade, Melbourne, VIC 3010

Directions:
To The Dax Centre from State Library Victoria

- Walk along La Trobe Street to the corner of La Trobe Street and Elizabeth Street
- Take Tram 19 - North Coburg (Note this trip is outside of the Free Tram Zone and regular fares will apply)
- Exit the tram at Stop 11 – University of Melbourne/Royal Parade



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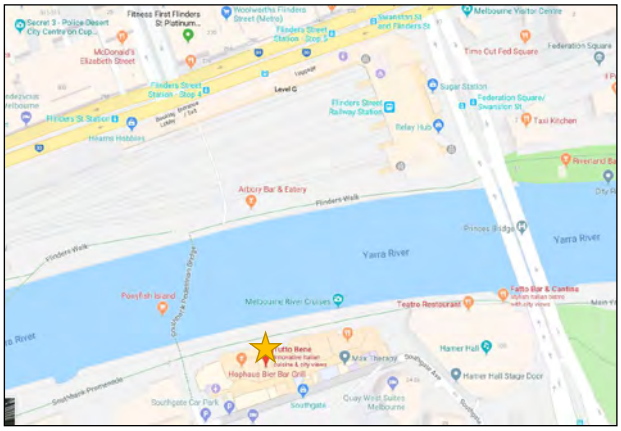
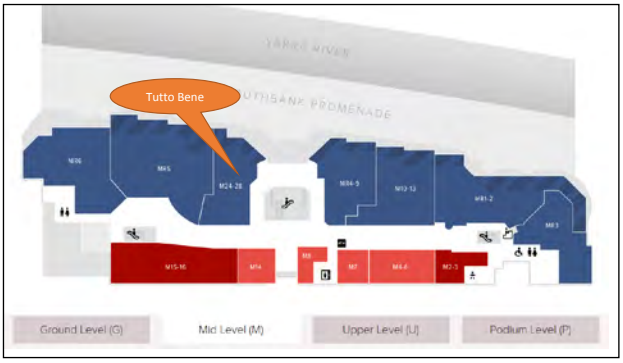
3 Conference Dinner (29th August)

The Conference Dinner will be held in:

Tutto Bene Restaurant
M28/3 Southgate Ave, Southbank VIC 3006

Directions:
Enter Southgate from Southbank Promenade and follow the escalator up to Mid Level. The restaurant is located on Mid Level, next to the escalator.



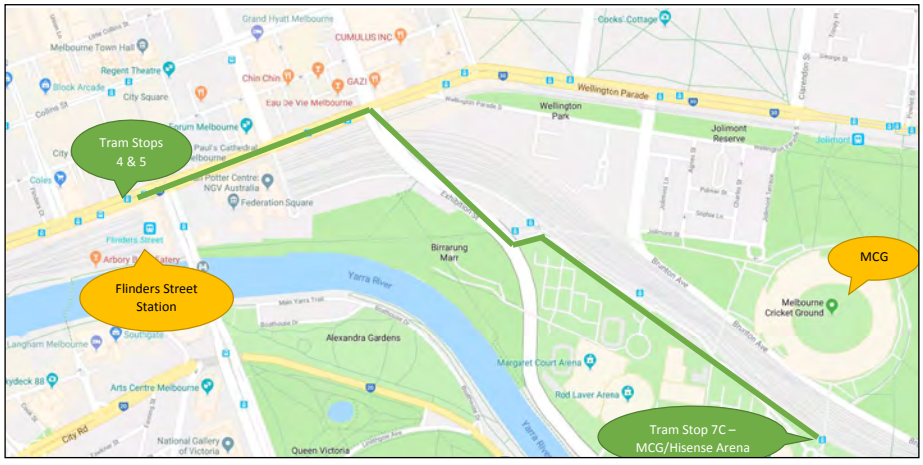


4 Educational Day (30th August)

The Educational Day sessions will be held at:

Melbourne Cricket Ground
Brunton Ave, Richmond, Melbourne, VIC 3002

Directions:
Please Enter the MCG through Gate 3
(Follow signs for NBPSA or SSBP)



Suggested Places for Lunch and Coffee

For Food

There are a range of food options in the **food courts of Melbourne Central** (corner La Trobe and Swanston Streets), **QV** (corner Lonsdale and Swanston Streets), and **Emporium** (287 Lonsdale Street), all of which are within easy walking distance of the State Library.
Other local options include:

1. **Darac** (51 A'Beckett Stret) - *Japanese/Korean cuisine*
2. **Izakaya Chuji** (165 Lonsdale Street) - *Japanese cuisine*
3. **Mr Tulk** (underneath the State Library) - *Café fare – sandwiches, salads, etc.*
4. **Stalactites** (177/183 Lonsdale Street) - *Greek cuisine*
5. **Father's Office** (249 Little Lonsdale Street, overlooking the State Library) - *American cuisine*
6. **Urban Fox** (309 Lt Lonsdale Street) - *Cafe fare (e.g. soups, sandwiches)*
7. **In A Rush** (380 Lonsdale Street) - *Soups, sandwiches, and wraps*

For Coffee

The State Library of Victoria is within walking distance of several of Melbourne's (many) excellent cafes, including:

1. **Mr Tulk** (underneath the State Library)
2. **Urban Fox** (309 Lt Lonsdale Street)
3. **Druids Café** (409 Swanston Street)
4. **Citi Espresso** (389 Swanston Street)
5. **Coffee Nomad** (376 Bowen Street)
6. **Little Rogue Coffee** (12 Drewery Lane)
7. **Lt. Nic** (262 Lonsdale Street)
8. **STREAT** (Melbourne Central Ground Floor, 211 La Trobe Street)

Keynote Speaker Profiles: Research Symposium *(in order of presentation)*

Associate Professor David Godler

Dr David Godler of the Murdoch Children's Research Institute (MCRI) and University of Melbourne, Department of Paediatrics, is a molecular geneticist by training whose work focuses on unravelling mechanisms of neurodevelopmental disorders and the development of novel diagnostic and screening techniques. David completed his PhD in 2007 at the Department of Medicine, Monash University, and has held post-doctoral fellow positions at MCRI in the laboratories of Professor Andy Choo and Dr Howard Slater. Since 2016 he has been Group Leader of Cyto-Molecular Diagnostics Research Laboratory at MCRI, regularly publishing in high quality specialty journals such as Clinical Chemistry, Neurology, JAMA Neurology, Genetics in Medicine and Human Molecular Genetics.

Using the clinical resources of Victorian Clinical Genetics Services, Royal Children's Hospital and those of national and international collaborators, his work centres on improved diagnosis of chromosomal abnormalities and epigenetic disorders associated with intellectual disability and autism. David also heads the world's largest fragile X syndrome prevalence study in 100,000 newborns (NHMRC funded), and a Prader-Willi syndrome newborn screening pilot to provide evidence regarding expanding current newborn screening in Australia and internationally. He is also the PI on DNA methylation studies that are utilising droplet digital PCR to detect low level mosaicism testing in developmental delay referrals of unknown cause. In 2018, David was awarded a Next Generation Clinical Researchers Program - Career Development Fellowship, funded by the Medical Research Future Fund (MRFF). The 4 year fellowship will investigate significance of low-level mosaicism to intellectual disability and autism in paediatric disorders.

Dr Tony Simon

Dr. Simon is a pediatric cognitive neuroscientist. His research focuses on the interactions between neural, cognitive, affective and stress biology differences in young people with genetic disorders that produce learning difficulties, behavioral dysregulation and psychopathology. Dr. Simon has spent over a decade and a half investigating how dysfunction in specific neurocognitive processing systems, such as attention, and spatial or temporal processing generates cognitive impairments in thinking about space, time, numbers as was as real world challenges like math, using money and navigation. He has developed and is testing a digital neurotherapeutic intervention (in the form a video game) to minimize such disability.

Dr. Simon's current main project is a National Institute of Mental Health funded longitudinal study on risk and protective factors for psychosis proneness in chromosome 22q11.2 deletion (Velocardiofacial/DiGeorge) syndrome based on the interaction of neurocognitive and affective processing and stress reactivity. Besides experimental cognitive processing analyses, Dr. Simon uses cutting edge neuroimaging methods, such as resting state functional magnetic resonance imaging (rs-fMRI), Diffusion Tensor Fiber Tracking as well as Event-Related Potential (ERP) components of electrophysiological studies in order to study the structure, function and connective patterns in the developing brain.

Associate Professor Melanie Porter

Associate Professor Melanie Porter has extensive research, teaching and clinical expertise in the field of neurodevelopmental disability. She is founder and co-director of the Centre for Atypical Neurodevelopment at Macquarie University, co-directs the clinical neuropsychology programs at Macquarie University and is a practicing Paediatric Neuropsychologist.

After completing her PhD on the neuropsychological profiles of individuals with Williams syndrome, autism spectrum disorder and Down syndrome in 2004, she has worked clinically part-time in both the private and public sectors, while taking up a postdoctoral position in 2005, then an academic post in 2008 to continue her research in the field.

Melanie currently leads an international, trans-disciplinary program of research into Williams syndrome and other neurodevelopmental disabilities (e.g., autism spectrum disorder, Fragile X syndrome, Down syndrome, 22q deletion syndrome, Neurofibromitosis Type 1) with 25+ national and international collaborators, 50+ peer review publications, and over 1,000 citations of her work. She has supervised over 40 postgraduate research students to completion and investigates the links between genetic, neuropsychological and brain impairment.

Her work includes detailed genotyping, neuropsychological testing, structural (MRI, DTI) and functional (MEG, fMRI) brain imaging, eye-tracking, neurological examinations and mouse models to explore the role of individual genes on brain development and subsequent cognitive, behavioural, social, psychological and motor function. Her work has been supported by Williams syndrome Australia Limited, Australian Rotary Health, the APEX Foundation and the Jerome Lejeune Foundation.

Melanie has a number of advisory, editorial and community roles in the field of neurodevelopmental disability and has been invited to present her work and to write medical and education guidelines as an expert in her field.

Professor Liz Pellicano

Liz Pellicano is Professor at Macquarie University, Sydney, Australia, having previously been Director of the Centre for Research in Autism and Education (CRAE) and Professor of Autism Education at University College London. She trained as a developmental and educational psychologist at the University of Western Australia, where she also completed her PhD on the cognitive profile of autistic children, before becoming a Junior Research Fellow in Psychiatry at the University of Oxford, UK, and Lecturer in Experimental Psychology at the University of Bristol, UK. In 2009, she was appointed Senior Lecturer at CRAE at UCL Institute of Education, University College London, UK. She became Director of CRAE in 2013 and Professor of Autism Education in 2015. In late 2017, she took up a Professorship in the Department of Educational Studies at Macquarie University in Sydney.

Much of Liz's research is focused on understanding the distinctive opportunities and challenges faced by autistic children, young people and adults, and tracing their impact on everyday life – at home, at school and out-and-about in the community. She has a passionate belief in community engagement in research, and is consistently dedicated both to ensuring that the outcomes of her research are as influential as possible in education and policy-making and to enhancing public understanding, and acceptance, of autism.

Keynote Speaker Profiles: Educational Day *(in order of presentation)*

Professor Petrus de Vries

Petrus de Vries is the Sue Struengmann Professor of Child & Adolescent Psychiatry, and Director of the Centre for Autism Research in Africa (cara.uct.ac.za) and the Adolescent Health Research Unit (ahru.uct.ac.za) at the University of Cape Town. He trained in Medicine at Stellenbosch University in South Africa before moving to the UK where he completed his clinical training in Psychiatry and Child & Adolescent Psychiatry, and a PhD in Developmental Neuroscience at the University of Cambridge. He returned to South Africa in 2012.

The Centre for Autism Research in Africa (CARA) is interested in screening, diagnosis, interventions, health/education systems and technology for autism in low-resource environments such as in Africa. The Adolescent Health Research Unit (AHRU) focuses on adolescent sexual and reproductive health, adolescent mental health, intimate partner violence, bullying, and health systems for young people. The Tuberous Sclerosis Complex (TSC) programme focuses on TSC-associated neuropsychiatric disorders (TAND).

Petrus was chairman of the Society for the Study of Behavioural Phenotypes (SSBP) from 2008 – 2017, and was on the WHO ICF-CY steering group for autism spectrum disorders and ADHD, under the chairmanship of Prof Sven Bolte. He is on the Executive of the International Association for Child & Adolescent Psychiatry and Allied Professions (IACAPAP) where he coordinates the Helmut Remschmidt Research Seminars, an international research capacity-building programme. He is chairman of the African Division of the Royal College of Psychiatrists, and is President-Elect of the South African Association for Child & Adolescent Psychiatry and Allied Professions (SA-ACAPAP). He is on the editorial boards of *Autism Research and Journal of Intellectual Disability Research* and is Associate Editor of the *Journal of Child & Adolescent Mental Health*.

The Centre for Autism Research was awarded the inaugural INSAR (International Society for Autism Research) Cultural Diversity Research Award in 2018, and Petrus was made an INSAR Fellow also in 2018.

A/Prof Honey Heussler

Dr Honey Heussler is a Developmental and Behavioural Paediatrician with dual Sleep Physician qualification. She is an Associate Professor with the University of Queensland and is Director of Developmental Paediatrics and Medical Director, Child Development Services as well as clinical responsibility in Behavioural and Sleep clinics with Children's Health Queensland

Dr Jonathan Cohen

Dr Jonathan Cohen is a parent and medical practitioner in private practice in Melbourne, Australia. He holds a Postgraduate Masters Degree in Family Medicine and is an Adjunct Senior Research Fellow with the Centre for Developmental Disability Health Victoria, Monash University Department of General Practice. He is the Medical Director of the Fragile X Alliance Clinic, Genetic Clinics Australia. He is involved with numerous research projects, author of multiple articles for medical, allied health journals and the lay press and presents regularly throughout Australasia on Fragile X Syndrome.

Professor Stewart Einfeld

Stewart Einfeld is Professor at the Brain and Mind Centre at the University of Sydney. He conducts research in developmental disabilities, focussing on behavioural and emotional problems, across neuroscience, clinical and public health domains. As a child and adolescent psychiatrist he provides mental health consultations mainly in the neurodevelopmental field.

Dr David Amor

David is a consultant clinical geneticist and clinician scientist with a research focus on human genetics. In 2016 he was appointed to the position of inaugural Galli Chair in Developmental Medicine, with a specific research and clinical focus on the causes of intellectual and physical disability. David completed RACP training in paediatrics and clinical genetics in 2000 before undertaking PhD studies in chromosome biology completed in 2004. Since 2005 he has worked as a consultant clinical geneticist at Victorian Clinical Genetics Services (VCGS) and as a Research Group leader at Murdoch Children's Research Institute (MCRI). From 2009 to 2016 he was Director of Victorian Clinical Genetics Services. David has been an author on more than 150 peer reviewed publications, five book chapters, and is a co-author in the 5th edition of Gardner and Sutherland's Chromosome Abnormalities and Genetic Counselling.

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Heather Renton

Heather is the President and Founder of Syndromes Without a Name (SWAN) – Australia. SWAN provides information and support to families caring for a child with an undiagnosed or rare genetic condition. Heather is the mother two children, Dominic 15 years old and Becky 11 years old. Becky was diagnosed with a rare genetic condition, FOXP1 syndrome at the age of 9 after being misdiagnosed twice with life threatening conditions. Heather is a passionate advocate for families who have children with undiagnosed and rare genetic conditions.

Heather is a member of the Melbourne Genomics Health Alliance Community Advisory Group and the Australian Genomics "Genomics in the Community" Working Group. She is a moderator for both the FOXP1 and Undiagnosed rareconnect.org communities.

Heather is co-founder and Director of Self Management Support, which empowers people to self-manage their own or their child's NDIS package.

Heather received a Highly Commended in the Service category at the 2017 Premier's Volunteer Champions Awards. The Melbourne Genomics Community Advisory Group (CAG), which she is an active member won the 'Outstanding Achievement by a Volunteer – Better Care Victoria Innovation Award' in the 2017 at the Minister for Health Volunteer Awards. Heather is one of the co-authors on the report "An Ounce of Prevention", which captured the value of early community engagement and co-design of projects. Heather received a scholarship to the Women's Board Leadership Mentoring Program for the period 2017/2018.

Dr Ainsley Newson

Dr Ainsley Newson is Associate Professor of Bioethics and Deputy Director at Sydney Health Ethics, the University of Sydney. She has worked in bioethics for nearly two decades, and has held academic positions in the United Kingdom and Australia. Her research focuses on emerging technologies, specifically on ethical aspects of genetics, genomics and their application in reproductive decision-making and in paediatrics. Her primary methodology is theoretical bioethics, but she also works with qualitative and quantitative researchers. Ainsley holds multi-disciplinary qualifications, with a PhD in Bioethics from the University of Melbourne and Bachelor degrees with honours in Science (majoring in human genetics) and Law (majoring in medical law and intellectual property). She has been funded by the National Health and Medical Research Council (Australia), the Australian Research Council, the European Union, the Wellcome Trust and the National Institutes of Health Research (UK). She is currently Ethics Lead within the Australian Genomics Health Alliance. She also co-chairs the Education, Ethics and Social Issues Committee of the Human Genetics Society of Australasia, among other service roles. Ainsley is also a regular media and public commentator on ethical issues in genetics, genomics and emerging biotechnologies.

Research Symposium Programme

Research Symposium

Venue: State Library Victoria

Day One – Research Symposium: Tuesday 28th August 2018	
08:00 - 08:45	**Registration and Poster Set-up**
08:45 - 09:00	**Welcome from the Conference Organisers**
09:00 - 09:15	**Welcome to Country**
SESSION 1: (Chair: *A/Prof Honey Heussler*)	
09:15 – 10:00	**Keynote 1:** *David Godler* – Novel Molecular and Clinical Aspects of FMR1 in Fragile X Syndrome Highlighting Significance of Mosaicism.
10:00 - 10:30	**Free Communications** (12 min + 3 min Q&A)
	Talk 1: *C.M. Kraan* – FMR1 Allele Size Distribution in 35,000 Males and Females: A Comparison of Developmental Delay and General Population Cohorts
	Talk 2: *E. Baker* – FMR1 mRNA in Blood as a Predictor of Intellectual Functioning and Autism Severity in Fragile X Syndrome: Is There a Difference Between Sexes?
10:30 - 11:00	**Morning refreshments and Poster Viewing**
SESSION 2: (Chair: *Prof Petrus de Vries*)	
11:00 - 11:45	**Free Communications** (12 min + 3 min Q&A)
	Talk 3: *R. Hagerman* – A Controlled Trial of Sertraline in Children 2 To 6 With ASD Without Fragile X Syndrome
	Talk 4: *S. Huijbregts* – The Impact of Metabolic Control and Tetrahydrobiopterin Treatment on Health Related Quality of Life of Patients with Early-Treated Phenylketonuria
	Talk 5: *F. Tassone* – Global Methylomic Profiling in Children with Autism Spectrum Disorders
12:00 - 13:00	**Time to enjoy lunch from local cafes or shops**
13:00 - 13:30	**Poster Viewing**
SESSION 3: (Chair: *Prof Flora Tassone*)	
13:30 - 14:15	**Keynote 2:** *Tony Simon* – The Impact of Cognitive-Affective Interactions on Risk and Protection for Psychosis Symptoms in Youth With 22q11.2DS
14:15 - 15:15	**Free Communications** (15 min + 5 min Q&A)
	Talk 6: *L. Campbell* – Emotion Dysregulation in 22q11.2 Deletion Syndrome
	Talk 7: *K. McCabe* – Social Impairment in 22q11.2 Deletion Syndrome: A Comparison With Idiopathic Autism Spectrum Disorder
	Talk 8: *D. McDonald-McGinn* – Are Language Scores an Early Predictor of Conversion to Psychosis?
15:15 - 15:45	**Afternoon refreshments and Poster Viewing**

Day One – Research Symposium: Tuesday 28th August 2018	
SESSION 4: (Chair: *Prof Anna Jansen*)	
15:45 - 16:25	**Free Communications** (15 min + 5 min Q&A)
	Talk 9: *P. Howlin* – Interventions for Children with Autism: Identifying What Works for Whom
	Talk 10: *L.P. Lawson* – Gender Differences in Internalising Psychopathology Among Young Adults on the Autism Spectrum
16:25 - 17:10	**Keynote 3:** *Melanie Porter* – Biological and Environmental Contributions to Cognition, Behaviour and Emotion in Williams Syndrome: Making Sense of a Complex Phenotype
	Close of Day 1
18:30	**Conference Reception –** The Dax Centre

Day Two – Research Symposium: Wednesday 29th August 2018	
08:15 - 08:45	**Registration** (For those attending Day 2 only)
08:45 - 09:00	**Welcome**
SESSION I: (Chair: *Prof Pat Howlin*)	
09:00 - 09:45	**Keynote 4:** *Liz Pellicano* – Knowing Autism
09:45 – 10:30	**3 Free Communications** (12min + 3min Q&A)
	Talk 11: *A. Jansen* – Top 15 Research Priorities in Tuberous Sclerosis Complex
	Talk 12: *D. Adams* – Hopes, Fears and Beliefs About Clinical Trials for Children with Angelman Syndrome, 22q11.2 Deletion Syndrome and Other Rare Genetic Disorders
	Talk 13: *R. Cvejic* – Does Administrative Health Data Have a Place in Behavioural Phenotype Research?
10:30 - 11:00	**Morning refreshments and Poster Viewing**
SESSION 2: (Chair: *Dr Dawn Adams*)	
11:00 – 11:45	**3 Free Communications** (12min + 3min Q&A)
	Talk 14: *R. Royston* – Cross-Syndrome Comparison of Psychopathological Risk Factors in Williams Syndrome, Fragile X Syndrome and Prader-Willi Syndrome
	Talk 15: *L. Groves* – The Prevalence and Profile of Anxiety Disorders in Cornelia de Lange and Fragile X Syndromes
	Talk 16: *J. Waite* – Emotional Dysregulation, Low Mood and Anxiety in Rubinstein- Taybi Syndrome

Day Two – Research Symposium: Wednesday 29th August 2018	
11:45 - 12:00	**A Short Presentation about SSBP Birmingham 2019**
12:00 - 13:00	**Time to enjoy lunch from local cafes or shops**
13:00 - 14:00	**SSBP AGM and Award Ceremony**
SESSION 3: (Chair: *Prof Stewart Einfeld*)	
14:00 – 15:00	**3 Free Communications** (15 min + 5 min Q&A)
	Talk 17: *K. Gray* – A Community-Based Parenting Intervention for Parents of Children with a Disability: Comparison of Effectiveness for Children With and Without Autism Spectrum Disorder
	Talk 18: *E. Pearson* – Communication in Angelman Syndrome: An Isolated Problem of Speech Production?
	Talk 19: *H. Heussler* – Meeting Developmental Milestones in Angelman Syndrome: Wide Age Ranges and Phenotypic Involvement
15:00 - 15:30	**Afternoon Refreshments and Poster Viewing**
SESSION 4: (Chair: *A/Prof Honey Heussler*)	
15:30 - 16:30	**Tom Oppé Distinguished Lecture:** *Professor Bruce Tonge* – School Non-attendance in Young People With Developmental Disabilities: The Need for Better Recognition
16:30 - 16:55	**Questions and Discussion**
16:55 - 17:00	**Close of Research Symposium**
19:30	**Gala Dinner – Tutto Bene Restaurant**

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Educational Day Draft Programme

Educational Day – NPBSA/SSBP

Venue - Melbourne Cricket Ground

This Draft Programme is provided as a guide only. The Educational Day is being run in conjunction with the NBPSA. On arrival, you will be able to download the NBPSA conference app, which will supercede the draft programme in this book. Alternatively, please see the NBPSA conference website for current information

Day Three – Educational Day: Thursday 30th August 2018		
08:00 - 08:45	**Arrival and Registration** Registration will be held in the Olympic Lounge, Level 3, Olympic Stand, Melbourne Cricket Ground (enter via Gate 3)	
08:45 - 09:15	**Welcome**	
09:15 - 10:15	**Keynote:** *Petrus de Vries* – Tuberous Sclerosis: Associated Neuropsychiatric Disorders (TAND)	
	TRACK 1	**TRACK 2**
10:45 - 11:15	*Honey Heussler* – Medicinal Cannabis in Neurodevelopmental Disorders: Myths and Hype	*Tony Simon* – How cognition-emotion interactions affect risk & protection for mental health diagnoses in children with 22q11.2 deletion syndrome
11:15 - 11:45	*Jonathan Cohen* – Fragile X Syndrome – Understanding Genes and Humanity	*Stewart Einfeld* – Case Presentations: Prader Willi, Williams, 22q11 - Understanding Behaviour in a Syndromic Context
11:45 - 12:15	*Gaby Dabscheck* – Neurofibromatosis	*Felicity Williams* – Angelman's Syndrome: A Parent and Professional Journey
12:15 - 13:15	**Lunch**	
Plenary Session: Gene Genie: Clinical, Ethical and Insurance Implications of Genetic Testing in Children with Neurodevelopmental Disorders		
13:30 - 13:40	*Heather Renton* – The patient journey: Welcome to Limbo Land	
13:40 - 14:05	*David Amor* – State of the Art Genetic Testing in Children with Neurodevelopmental Disorders	
14:05 - 14:20	*Martin Delatycki* – Insurance Implications of Genetic Testing	
14:20 - 15:00	**Panel Discussion:** *Ainsley Newson, Teresa Lazzaro, Ivan Macciocca* – Legal and Ethical Implicaitons of Genetic Testing	
15:00 - 15:30	**Afternoon Tea**	
15:30	**End of Day for SSBP Registrants**	

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Abstracts for Research Symposium Oral Presentations *in order of presentation*

KEYNOTE 1: Novel molecular and clinical aspects of FMR1 in Fragile X Syndrome highlighting significance of mosaicism

Solange Aliaga [1,2,3], Emma Baker [1], Claudine Kraan, Marta Arpone [1, 2], Quang M Bui [4,] Xin Li [1,] Ling Ling [1] David Francis, MS [5], Mathew Hunter [7,8], Justine Elliot [5], Carolyn Rogers [6], Mike Field [6], Howard R Slater PhD [1,5], Lesley Bretherton [2,1], Lorena Santa Maria [3], Víctor Faundes [3], Bianca Curotto [3], Paulina Morales [3], Cesar Trigo [3], Isabel Salas [3], Angelica M. Alliende [3], David Amor [1,2], ***David E Godler*** *[1,2]*

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Background: Fragile X syndrome (FXS) is a common single gene cause of intellectual disability and autism phenotype, caused by loss of FMR1 protein (FMRP). Increased intragenic FMR1 DNA methylation (DNAm) of the Fragile X Related Epigenetic Element 2 (FREE2) in blood and epithelial cells has been correlated with FMRP and lower intellectual functioning in FXS males and females. This study examined relationships between the above parameters and autism phenotype in FXS males.

Methods: The study cohorts included 95 males with fragile X (FXS) (age range 0.5 – 43 years). The main measures of: (i) cognition were Wechsler Scales selected according to age criteria; (ii) social and communicative behaviour was the Autism Diagnostic Observation Schedule (ADOS-2). Methylation Specific Quantitative Melt Analysis (MS-QMA) (analytical sensitivity 2%), EpiTYPER system (analytical sensitivity 10%) and methylation sensitive Southern blot (SB) (analytical sensitivity 20%) were used to characterise FMR1 promoter DNAm. in blood, buccal epithelial cell (BEC) and saliva DNA with mosaicism defined as methylation < 100%.

Results: MS-QMA significantly correlated with IQ scores in all tissues tested, with the strongest relationships found for blood DNA and Verbal IQ (VIQ) ($p=1.7\times10-5$; n=45). Importantly, for the paediatric sub-group (<18 years), FREE2 DNAm in blood showed significant relationships with ADOS Calibrated Severity Score: MS-QMA (p=0.03; n=33) and EpiTYPER system (p=0.003; n=31). Interestingly, all males were found to be methylation mosaics with MS-QMA, while for SB this was only ~80%. Of the 12 FM males 100% methylated by SB, only 3 (25%) had complete silencing of FMR1 mRNA. MS-QMA showed the strongest relationships with FMR1 mRNA levels in blood ($p=2.4\times10-8$; n=69).

Conclusions: Reduction in intellectual functioning and presence of a co-morbid autism phenotype, as well as decrease in FMR1 mRNA levels (rather than silencing), have been linked to methylation mosaicism at the FREE2 region in this study.

Keywords: Fragile X syndrome, DNA methylation, epigenetics, autism, intellectual disability

TALK 1: FMR1 Allele Size Distribution in 35,000 Males and Females: A Comparison of Developmental Delay and General Population Cohorts

Kraan C.M. [1,2,3], *Bui Q.M.*[4], *Field M.*[5], *Archibald A.D.*[6], *Metcalfe S.M.*[2,7], *Bennetts B.H.*[8], *Wotton T.L.*[8,9], *Amor D.J.1,* [2,10], *Francis D.*[1] *and Godler D.E.*[1,2]

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Background: Developmental delay phenotypes have been associated with *FMR1* premutation (PM: 55–200 CGG repeats) and "gray zone" (GZ: 45–54 CGG repeats) alleles. However, these associations have not been confirmed by larger studies to be useful in paediatric diagnostic or screening settings.

Methods: This study determined the prevalence of PM and GZ alleles in two independent cohorts of 19,076 paediatric referrals to developmental delay diagnostic testing through Victorian Clinical Genetics Service (cohort 1: N = 10,235; cohort 2: N = 8841), compared with two independent general population cohorts (newborn screening N = 1997; carrier screening by the Victorian Clinical Genetics Service prepair program N = 14,249).

Results: PM and GZ prevalence rates were not significantly increased ($p > 0.05$) in either developmental delay cohort (male PM: 0.12–0.22%; female PM: 0.26–0.33%; male GZ: 0.68–0.69%; female GZ: 1.59–2.13-%) compared with general population cohorts (male PM: 0.20%; female PM: 0.27–0.82%; male GZ: 0.79%; female GZ: 1.43–2.51%). Furthermore, CGG size distributions were comparable across datasets, with each having a modal value of 29 or 30 and ~ 1/3 females and ~ 1/5 males having at least one allele with ≤ 26 CGG repeats.

Conclusion: These data do not support the causative link between PM and GZ expansions and developmental-delay phenotypes in paediatric settings.

Key Words: Developmental delay (DD); fragile X mental retardation 1 gene (*FMR1* gene); fragile X syndrome (FXS); premutation; prevalence.

TALK 2: FMR1 mRNA in Blood as a Predictor of Intellectual Functioning and Autism Severity in Fragile X Syndrome: Is There a Difference Between Sexes?

Baker E.K. [1], *Arpone M.* [1,2], *Aliaga S.* [1,2], *Bretherton L.* [3], *Bui M.*[4], *Kraan C.* [1,5,6], *Alliende A.* [7], *Rogers C.* [8], *Amor D.J.* [1,6,9] *and Godler D.E.*[1,6]

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Background: Fragile X Syndrome (FXS) is a common single gene cause of intellectual disability and co-morbid autism spectrum disorder (ASD). FXS is caused by a large trinucleotide CGG expansion (>200 repeats) within the *FMR1* gene located on the X chromosome. FM alleles are associated with epigenetic changes that result in decreased production of *FMR1* mRNA and loss of the *FMR1* protein FMRP. Males with FXS typically present with a more severe phenotype compared to females, however the biomarkers that underlie differences in both sexes have not been defined.

Methods: 125 individuals (28% female) with FXS aged between 1 and 43 years recruited from Australia and Chile participated in the study. The Autism Diagnostic Observation Schedule-2nd Edition (ADOS-2) was used to assess symptoms associated with ASD while cognitive functioning was assessed with the Mullen Scales of Early Learning (< 3 years), and an age appropriate Wechsler scale (Verbal IQ [VIQ], Performance IQ [PIQ] and Full Scale IQ [FSIQ]).

Results: Genotype-phenotype analyses showed that *FMR1* mRNA levels in blood were strongly associated with FSIQ (p <.001; n = 41), VIQ (p =.029; n = 41) and PIQ (p =.002; n= 43) in males, but not in females (FSIQ: p =.394, n = 24; VIQ: p =.170; n = 25; PIQ: p =.438; n = 25). In contrast, *FMR1* mRNA levels were strongly associated with total Calibrated Severity Scores in females (p =.001; n =.001), but not males (p =.284; n = 59)

Conclusion: This study shows that *FMR1* mRNA levels in blood are associated with symptoms of ASD in females and intellectual functioning in males with FXS. This dissociation by gender in the relationships between *FMR1* expression with type and severity of intellectual functioning and behavioural phenotypes warrants further study.

Keywords: *FMR1* mRNA; Fragile X; Autism; IQ.

TALK 3: A Controlled Trial of Sertraline in Children 2 to 6 With ASD Without Fragile X Syndrome

Hagerman R. [1,2], *Potter L.* [1,2], *Biag H.* [1], *Scholze D.* [1,2], *Schneider A.* [1,2], *Rivera S.M.* [1,3] *and Tassone F.* [1,4]

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[4] *UCDMC Department of Biochemistry and Molecular Medicine, USA*

Background: There is evidence of low serotonin production in the CNS of young children with Autism Spectrum Disorder (ASD). Metabolomics studies demonstrate a depletion of the enzymes that metabolize tryptophan to serotonin in children with ASD. A 6-month controlled trial of low dose sertraline in children with fragile X syndrome (FXS) demonstrated efficacy on subtests of the Mullen (MSEL) vs placebo. The current study follows a similar protocol in ASD.

Methods: 58 children with ASD ages 24 to 72 months (mean 50 SD 11.66) were enrolled in a 6-month double-blind controlled trial of low dose sertraline (2.5 to 5.0 mg/d). Primary outcome measures were the changes in MSEL expressive language raw score and combined age equivalent score. Additional measures included the CGI-I, VAS, ABC, SPMP, SRS2, PAS-R, VABSII and PLS5. Molecular biomarkers including the BDNF allelic variants were assessed. At enrolment, all children were receiving interventions from school/therapists for ASD.

Results: 6 patients discontinued the study due to adverse events (3 hyperactivity, 1 increased aggression, 1 diarrhoea, 1 excessive screaming). Of 227 adverse events to date, all were mild or moderate except one serious adverse event (hospitalization for viral URI complications) that was not related to study drug. Many children demonstrated a positive response to the study, including parent-reported effects on behaviour and language. Unblinding will occur in July 2018 when the last patient completes the trial. Analysis of the efficacy data will be presented at the SSBP conference.

Conclusion: The response of children with ASD to low dose sertraline, including safety and overall efficacy, will be presented. Anticipated benefits will likely be in language and anxiety reduction. Molecular biomarkers may correlate with outcome.

Keywords: ASD, Treatment, sertraline.

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TALK 4: The Impact of Metabolic Control and Tetrahydrobiopterin Treatment on Health Related Quality of Life of Patients With Early-Treated Phenylketonuria

Huijbregts S.C.J. [1]***, Bosch A.M.*** [2]***, Simons Q.A.*** [1]***, Jahja R.*** [3] ***and Van Spronsen F.J.*** [3]

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[3] *Division of Metabolic Diseases, University Medical Center Groningen, Groningen, the Netherlands.*

Background: The aim of the present study was to examine Health-Related Quality of Life (HRQoL) of patients with Phenylketonuria (PKU) in three different age groups and to investigate the impact of metabolic control and tetrahydrobiopterin (BH4) treatment on HRQoL of these patients. BH4 is a cofactor of the Phenylalanine Hydroxylase (PAH) enzyme, which is deficient in PKU. PAH is required for the conversion of phenylalanine (Phe) into tyrosine, which, in turn is a metabolic precursor of dopamine.
Methods: Participants were 90 early-treated patients aged 7 to 40 years (M=21.0, SD=10.1) and 109 controls aged 7 to 40.8 years (M=19.4, SD=8.6). HRQoL was assessed with the (generic) TNO-AZL questionnaires.
Results: Overall, good HRQoL was reported for children below 12 years of age, although they were judged to be less autonomic than their healthy counterparts. Adolescents aged 12 – 15 years showed poorer HRQoL in the domain "cognitive functioning" compared to controls. For adults ≥ 16 years, poorer age-controlled HRQoL was found for domains cognition, depressive moods, and anger, with a further trend for the domain "pain". With respect to metabolic control, only for adult PKU-patients robust associations were observed, indicating poorer functioning, most notably in the domains cognition, sleep, pain, sexuality and anger, with higher historical and concurrent Phe-levels. With respect BH4-use, effects on HRQoL were again only observed for adult PKU-patients. After controlling for age and historical Phe-levels, small but significant differences in favor of adult BH4-users compared to non-users were observed for HRQoL-categories happiness, anger, and social functioning.
Conclusion: Together, these results suggest that, even for generally well-controlled PKU-patients, HRQoL-problems become more evident with age, and that these problems are often related to metabolic control. Whereas BH4-effects are particularly observed for general mood and sociability, (history of) metabolic control is more strongly related to basic physical and cognitive functioning.

Keywords: Phenylketonuria (PKU), tetrahydrobiopterin (BH4), Health-Related Quality of Life (HRQoL), metabolic control, phenylalanine (Phe).

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TALK 5: Global Methylomic Profiling in Children With Autism Spectrum Disorders

Alolabi R.R. [1], *Tang H.-T.* [1], *Zhu Y.* [2], *Durbin-Johnson B.* [3], *Chedin F.* [4,5], *Hagerman R.* [6,7] *and* ***Tassone F.*** [1,6]

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[7] *Department of Pediatrics, UC Davis, Sacramento, CA, USA.*

Background: Autism Spectrum Disorder (ASD) is an early onset, developmental disorder with a reported incidence of 1 in 68 people as stated by the Centers of Disease Control and Prevention. DNA methylation, can play a role in the pathogenesis of ASD having a significant role in modulating gene expression. Indeed, it has been observed that genes that have a role in epigenetic pathways constitute a large percentage of the candidate risk genes for ASD.

Methods: Samples from 44 age-matched participants (2 – 5 years old) including 23 subjects with ASD and 11 neurotypically developing (TD) children were investigated. DNA methylation was determined using the Illumina Human Methylation EPIC Bead Chip. ANOVA with FDR was used to identify differentially methylated CG sites between groups. Gene expression levels in a subset of genes, were measured by qRT-PCR and compared between groups using ANOVA.

Results: Using a p-value of 0.05, we found that 76 genes were significantly hypermethylated, and 694 genes were significantly hypomethylated in children with ASD compared to TD. When using more stringent criteria with a p-value less than 0.05 and fold change in methylation higher than 1.5, we found that children with ASD had a total of 47 genes that were differentially methylated compared to TD including znf587, NF2 and the C11orf31 genes. Out of the 47 genes, 30 were hypermethylated and 17 hypomethylated. qRT-PCR experiments showed that the differential expression of a subset of genes was in line with their methylation status in all three groups.

Conclusion: This study shows a potential role for altered DNA methylation in the pathology of ASD and may help in the diagnostic classification of children with ASD based on epigenetic markers. In addition, it may pave the way for developing therapeutic interventions that could reverse the altered methylomic profile in children with neurodevelopmental disorders.

Keywords: epigenetics, methylation, ASD, expression.

KEYNOTE 2: The Impact of Cognitive-Affective Interactions on Risk and Protection for Psychosis Symptoms in Youth With 22q11.2DS

Professor Tony Simon
UC Davis MIND Institute.
UC Davis Department of Psychiatry & Behavioral Sciences.

Youth with chromosome 22q11.2 deletion syndrome struggle with a range of learning difficulties that, if not well matched to environmental requirements, contribute to functionally impairing anxiety. This interaction further contributes to other behavioral dysregulations such as inattentiveness that frequently results in an ADHD diagnosis. Our research has shown that anxiety and adaptive functioning are negatively correlated in children with 22q11.2D. The variability in this relationship led us to conceptualize an informal "coper-struggler" dimension along which individuals might be situated. Our research also shows that coper/struggler status is unrelated to the child's intellectual functioning. This led us to hypothesize that the amount of "allostatic load" associated with a decade-plus of childhood struggle (or lack of it) might explain some of the variance in psychosis-proneness symptomology that is manifested in late adolescence. We are now testing this hypothesis in a longitudinal study of that relates a range of bio-behavioral intermediate phenotypes of psychosis-proneness to gold standard measures of prodromal symptoms.

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TALK 6: Emotion Dysregulation in 22q11.2 Deletion Syndrome

Campbell, L.E. *[1], Swaab, L. [1], McCabe, K. [2], Simon, T. [2]*

[1] School of Psychology, Faculty of Health, University of Newcastle, Ourimbah, Australia

[2] Department of Psychiatry and Behavioral Sciences, UC Davis School of Medicine, UC Davis MIND Institute, USA

Background: Emotion regulation, also known as emotional self-control is the ability to regulate one's affect and emotions in response to environmental changes. Young people with 22q11.2 deletion syndrome (22q11DS) are at increased risk of psychiatric disorders associated with emotional dysregulation including anxiety. The current study aimed to investigate the rate of emotional dysregulation in young people with 22q11DS, and the associations with psychiatric comorbidity, compared with typically developing community controls.

Methods: The cross-sectional sample included 245 children, aged 4 – 22 years, including 129 diagnosed with 22q11DS and 116 typically developing controls recruited from the UC Davis MIND Institute. Parents completed the Behavior Assessment System for Children, Second Edition Parent Rating Scale (BASC-2) and the Adaptive Behaviour Assessment System, Second Edition (ABAS-II). Participants completed the Wechsler Scales of Intelligence.

Results: The 22q11DS sample had significantly higher scores on emotional self-control, indicating poorer ability to regulate emotions. More specifically, whilst only 9 (8%) participants in the TD group had elevated or clinically significant problems with emotional self-control, this applied to 64 (50%) of participants in the 22q11DS group. Within 22q11DS group analyses identified no age or gender differences between the participants with emotional dysregulation and those in the typical range. A trend level effect indicated that the average IQ was higher (77 vs. 73) in the elevated group ($p = .06$) although adaptive functioning was decreased compared to the group in the typical rage ($p = .013$). The group with the elevated emotional dysregulation had significantly higher rates of behavioural problems including anger control and aggressive behaviours.

Conclusion: Emotional dysregulation is not only associated with anxiety but also leads to an increased risk of externalising behaviour such as anger control in this population. Emotional dysregulation is common among young people with 22q11DS should be a key target for interventions to improve behavioural outcomes in this population.

Keywords: 22q11.2 deletion syndrome, emotion regulation, aggression, anger control

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TALK 7: Social Impairment in 22q11.2 Deletion Syndrome: A Comparison With Idiopathic Autism Spectrum Disorder

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Background: Behaviours characteristic of autism spectrum disorder (ASD) are common in 22q11.2 deletion syndrome (22q), and individuals with this deletion are diagnosed with ASD at higher rates compared with the general population. The current study sought to examine the causes of the social impairment seen in 22q by generating comparative perceptual, cognitive, linguistic, behavioural and emotional intermediate phenotype and comparing these with an age and IQ matched group of children with idiopathic ASD (iASD). It was expected that while superficially similar to iASD, social impairment in 22q would have a different etiology, despite similar level of intellectual functioning and significant social challenges.

Methods: Children aged 6 – 12 with either confirmed 22q (mean (SD) age: 9.3 (2.0); FSIQ: 84.0 (11.4)) or iASD (mean (SD) age: 9.6 (2.0); FSIQ: 84.1 (11.3)) were tested. Social Responsiveness Scale (SRS) and Social Communication Questionnaire (SCQ) screened participants for reciprocal social communication difficulties. Participants completed a clinician-blinded Autism Diagnostic Observation Schedule (ADOS Module 3) assessment with clinical best estimate (CBE). Measures of language (expressive/receptive, figurative and word generation), social cognition (theory of mind, emotion and gesture recognition) and executive functioning were collected.

Results: Item-level comparison of ADOS ratings indicated areas of convergence and divergence between the groups. In the 22q group 47% (8/17) reported clinically significant ADOS scores. Clinically significant scores on all SRS, SCQ and ADOS measures were present for 23% (4/17) of individuals with 22q, however, only 1 participant also yielded a CBE diagnosis of ASD. Group differences on measures of social cognition (gesture recognition) were not reported ($p>0.05$). Divergence in language profile was observed via interaction effect for expressive/receptive language ($p<0.05$).

Conclusion: We report evidence of divergent patterns in language abilities between 22q and iASD groups. Further, our findings suggest that parent reports such as the SRS may not be an effective predictor of the presence of ASD symptomatology in 22q.

Keywords: 22q11.2, social cognition, ASD, social phenotype, cognitive profile, social impairment.

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TALK 8: Are Language Scores an Early Predictor of Conversion to Psychosis?

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Background: Patients with 22q11.2 Deletion Syndrome (22q11.2DS) have a 25% chance of developing schizophrenia (SZ), recently reported to follow cognitive decline. We also noted a decline in language scores from pre-school to school aged children and created a "growth chart" of typical language development which we hypothesize may ultimately correlate with a pre-disposition to psychosis.

Methods: We performed a retrospective chart review of 730 children, ages 4 months-21 years, with a laboratory confirmed 22q11.2 deletion, followed in the 22q and You Center at the Children's Hospital of Philadelphia and evaluated by a Speech-Language Pathologist using the Pre-School Language Scale (PLS)/the Clinical Evaluation of Language Fundamentals (CELF), stratified by test and age. A logarithmic model was used to determine line of best fit.

Results: A significant decline in mean total test scores (MTTS) from pre-school to school age was observed. Specifically, the MTTS was 83.7 at 0-<5 years, 71.25 at 5-<10 years, 70.1 at 10-<15 years, and 66 at age 15-<20 years. The steepest decline occurred between 0-<5 years and 5-<10 years, while differences in later groups revealed a much lower rate of change. Conversely, a group of children followed longitudinally displayed an increase in scores over time.

Conclusions: We developed a novel "language growth chart" for patients with 22q11.2DS and, despite a known association with significant delays in emergence of language, our data revealed the highest language scores in young children, followed by a striking rate of decline in the school-aged years and plateauing at approximately age 10 years. Notably, we also identified a sub-cohort of children with an increase in language scores over time. Thus, we plan to compare this data to existing records on patients with and without cognitive decline and SZ, aiming to identify children with an increased risk for psychiatric disorders at an even earlier age.

Keywords: chromosome, 22q, deletion, schizophrenia, language, IQ

TALK 9: Interventions for Children With Autism: Identifying What Works for Whom

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Background: Despite the heterogeneity of autism, most intervention research focuses on group outcomes; little is known about the individual characteristics of children who do, or do not, respond to treatment.
Methods: We explored factors predictive of treatment response, as opposed to variables related to prognosis in autism more generally, in two large-scale data sets: (i) 152 pre-school children involved in a parent-mediated, social-communication randomised control trial (ii) 240 school-aged children receiving social-cognition interventions. The Reliable Change Index was used to identify children as responders or non-responders to intervention. Logistic regression was used to identify baseline variables predictive of treatment response.
Results: Group analyses indicated moderate-large improvements in each intervention group compared with treatment as usual (TAU). However, in both treatment and TAU conditions, some children failed to improve whilst others made considerable gains. None of the variables typically associated with a good prognosis in autism, such as cognitive, linguistic and social skills were predictive of treatment response. However, in the parent-mediated trial, TAU children in the site with greater social deprivation had a poorer outcome ($p < .01$) than TAU children in other sites. In the social-cognition cohort, children with poorer baseline social skills were more likely to respond to intervention ($p = .01$) than those with better developed social skills.
Conclusion: The findings illustrate the complexity and challenges of identifying factors related to individual responses to intervention; they also highlight the importance of distinguishing between prognostic indicators of natural improvement over time and variables that predict treatment outcome. To date, little is known about which children may benefit from a particular intervention or for whom it is contraindicated. Larger, multi-centre trials are essential to understand the variables related to treatment response and to enable educators and clinicians to choose appropriately individualised interventions for children with autism.

Key words: Autism; outcome; response to intervention.

TALK 10: Gender Differences in Internalising Psychopathology Among Young Adults on the Autism Spectrum

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Background: There is a growing body of literature regarding the impact of internalising psychopathology symptoms for adults on the autism spectrum. However, relatively little research has investigated whether the experience of anxiety or depression is different among males and females on the spectrum. The aim of this study was to explore any gender differences in internalising psychopathology among a sample of young adults on the spectrum.
Methods: Participants comprised of 111 young adults (78 male, 33 female) on the spectrum aged 15 to 24 years from the baseline survey of the Longitudinal Study of Australian School Leavers with Autism (SASLA). Respondents completed the battery of questionnaires online. The measures examined in this analysis included Autism Quotient-Short (AQ-28), DSM-V Dimensional Generalised Anxiety Disorder Scale (GAD-D), Patient Health Questionnaire-9 (PHQ-9), and Emotion Regulation Questionnaire (ERQ).
Results: An initial examination showed that despite no differences in overall Autism-Quotient scores, females had significantly higher levels of anxiety ($F(1,83) = 18.89$, $p<.001$, eta2=.14) and depression ($F(1,81) = 8.16$, $p=.005$, eta2=.09) compared to males on the spectrum. Further, it was found that a significantly higher proportion of females than males fell above the clinical cut-off on the GAD-D ($p=.003$) and PHQ-9 ($p=.031$). A hierarchical regression model was used to examine the relationship between emotion regulation and internalising psychopathology. It was found that among females, a higher emotion regulation ratio (i.e. greater use of emotional suppression relative to emotional appraisal) significantly predicted higher anxiety ($\beta=.630$, $p=.009$) and depression symptoms ($\beta=.912$, $p<.001$). No relationship was found for males on the spectrum.
Conclusion: These results add to the literature suggesting that females on the spectrum experience significantly more internalising psychopathology difficulties than males. The findings also indicate a difference between the genders on the relationship between emotion regulation strategies and internalising psychopathology, which has important implications for intervention strategies.

Keywords: autism spectrum disorder, gender, psychopathology.

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KEYNOTE 3: Biological and Environmental Contributions to Cognition, Behaviour and Emotion in Williams Syndrome: Making Sense of a Complex Phenotype

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Neurodevelopmental disorders affect brain development which, in turn, leads to complex interplays between cognition, behaviour and emotion. There are also environmental factors at play. With this in mind, we deconstruct and reconstruct the Williams syndrome phenotype exploring both typical profiles, as well as individual variability. The Williams syndrome phenotype, among other things, includes executive dysfunction, hypersociability and anxiety. Other neurodevelopmental conditions are compared and contrasted along the way.

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KEYNOTE 4: Knowing Autism

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Background: Autism affects millions of citizens in Australia and across the globe. Despite widespread public interest in autism, autistic people and their families have rarely been actively engaged in the research process. They have largely not been given the opportunity to decide research priorities, shape how an issue is researched, or help draw out practical lessons from research. Many have reported feeling disenfranchised as a result.
Methods: Developing ways to involve autistic people and their allies – in deciding which topic to research, the way an issue is researched, how it becomes funded, who undertakes the research and so on – is one key way both to rebuild feelings of trust and to ensure that a greater portion of research has a direct and sustained impact on those who need it most.
Results: Autism researchers do not do this enough – and indeed, scientists are often reticent about involving community members in their research. But can non-autistic scientists ever really understand what autistic people and their families need from their research? In this presentation, I will argue that truly understanding autism – knowing autism – requires both objective and subjective understandings, experiences and expertise, that is, listening, learning and involving autistic people and their families in research.
Conclusions: I will discuss in depth what the autistic community rightly demands of autism research and the major changes – in terms of genuinely inclusive, participatory research – that will need to be made to deliver on their expectations.

Keywords: autism, participatory research, inclusion, engagement

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TALK 11: Top 15 Research Priorities in Tuberous Sclerosis Complex

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Background: Tuberous sclerosis complex (TSC) is an incurable genetic condition that affects approximately 2 million people worldwide. Patients' lives are impacted by the threat of tumour growth and by the burden of refractory epilepsy, disfiguring skin lesions or TSC-associated neuropsychiatric disorders (TAND). Quality of life, burden of illness, and socio-economic impact of TSC are poorly researched.

Methods: Inspired by methods established by the James Lind Alliance, the University of Amsterdam and the Fondation Motrice France, a priority-setting partnership in TSC was established and a multi-stakeholder dialogue for setting research priorities was conducted. Research questions were developed based on input from all stakeholders using focus groups, individual in-depth interviews and an online, Delphi-type information exchange, completed with data from literature. Priority setting was carried out using online voting in combination with facilitated deliberation workshops.

Results: Focus groups and interviews with 24 patients and caregivers resulted in 350 uncertainties which were translated into 62 researchable questions. These were submitted for refinement and prioritization to a panel of representatives of six international patient organizations, resulting in 39 researchable questions and eight urgent needs. In parallel, individual interviews of 19 healthcare-practitioners and researchers resulted in a list of >250 uncertainties translated into 39 researchable questions, which were submitted for review and further input to 30 TSC experts. Integration of >200 comments and refinements led to 49 researchable questions which were then prioritized by online voting. The top 15 research priorities in TSC were agreed during a workshop that involved ten patients and caregivers as well as 11 researchers and healthcare practitioners.

Conclusion: These 15 priorities are intended to provide a platform for researchers, funding bodies, and industry to ensure that future research funding and research activities focus on questions that are important to patients and families with TSC as well as their healthcare-providers.

Keywords: tuberous sclerosis complex, multi-stakeholder dialogue, research priority setting, stakeholder participation

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TALK 12: Hopes, Fears and Beliefs About Clinical Trials for Children With Angelman Syndrome, 22q11.2 Deletion Syndrome and Other Rare Genetic Disorders

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Background: The rapid growth in genomic medicine has led to advances in potential treatments for a number of rare syndromes. However, little is known about what parents of children with such syndromes think and feel about these trials and their priorities for treatment.

Methods: Parents of 89 children with Angelman (n=42), 22q11.2 deletion syndrome (n=20) and other syndromes (n=27) completed an online survey. Questions asked about their knowledge and perspectives on clinical trials and the specific areas they feel should and should not be targeted by treatments.

Results: The majority (91%) felt that clinical trials aiming to reduce symptoms associated with their child's syndrome were positive, but there were significant differences between groups in the proportion that felt that such trials should be aiming to "cure" their child's syndrome ($x2(4)=28.9$, $p<.001$). Although less than half of parents reported feeling at least "moderately" confident in their knowledge about clinical trials, nearly half of the parents reported being keen to take part in clinical trials, even if the treatment had not been trialled in humans. Behaviour and IQ were identified as priority target areas by 33.3%-45% and 15 – 19% of parents (respectively) across all 3 groups. However, other target areas were syndrome-specific, with mental health being identified as a priority by 50% of the 22q11 group and speech/communication by 73.8% of the Angelman group. Almost one-third identified personality as the one characteristic they would not want to be changed.

Conclusion: This expands the limited knowledge on parent's perceptions and priorities for treatment trials. Parents of children with rare genetic syndromes are motivated and keen to take part in trials to reduce the symptoms of their child's syndrome, despite potentially not being fully informed of what this means. It is important that researchers, clinicians and trial coordinators work together to increase parental knowledge prior to trials commencing.

Keywords: syndrome, Angelman, 22q11, parents, trials.

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TALK 13: Does Administrative Health Data Have a Place in Behavioural Phenotype Research?

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Background: Behavioural phenotype studies typically involve direct observation or informant ratings of behavioural features associated with genetic syndromes. This study takes an alternative approach to investigate whether administrative health data can be used to delineate syndrome-specific patterns of morbidity that may be linked to known behavioural phenotypes. As a group, people with intellectual disability experience higher rates of accidents/injuries than the general population; identified risk factors include epilepsy, impulsivity, absence of speech and high sociability. Here we use hospital admissions data to determine the rates of different types of accidents/injuries among people with two distinct syndromes, Angelman syndrome (AS) and Down syndrome (DS), and compare these to the general population.

Methods: A retrospective cohort study of people with AS (n=492, 52% male) and DS (n=3,570, 53% male) aged 0 – 44 years who were admitted to hospitals in New South Wales (NSW), Australia, from 2002 – 2015. Direct standardised method was used to compare age-adjusted rates of hospitalisation for people with AS, DS, and the NSW general population.

Results: 26% and 12% of people with AS and DS, respectively, were hospitalised for accident/injury from 2002 – 2015. The age-adjusted rate for admission for any accident/injury was five times higher in AS (8,697/100,000 person years (PY)) than that in DS (1,774/100,000 PY) and the general population (1,847/100,000 PY). Rates of interpersonal violence and falls were also higher in AS (interpersonal violence=3,325/100,000 PY; falls=2,407/100,000 PY) than those for DS (interpersonal violence=552/100,000 PY; falls=489/100,000 PY) and the general population (interpersonal violence=1,743/100,000 PY; falls=1,844/100,000 PY).

Conclusion: Our findings show a double dissociation between admission rates for specific types of accidents/injuries between two genetic syndromes with contrasting behavioural phenotypes, with important implications for prevention planning. This provides preliminary evidence of the potential utility of administrative health data in the context of behavioural phenotype research.

Keywords: Angelman syndrome, Down syndrome, Accidents, Injury, Hospital admissions.

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TALK 14: Cross-Syndrome Comparison of Psychopathological Risk Factors in Williams Syndrome, Fragile X Syndrome and Prader-Willi Syndrome

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Background: Psychopathology is highly prevalent in adolescents and adults with several genetic syndromes associated with intellectual disability, including Williams syndrome (WS), fragile X syndrome (FXS) and Prader-willi syndrome (PWS). However, little is known about associated risk factors. This study aims to identify whether age, health difficulties, adaptive ability and sensory processing impairments may predict or influence psychopathology in these groups.

Methods: A questionnaire study was conducted with 111 parents/carers of individuals over the age of 12 (WS=35, FXS =50, PWS=26; 74 were male). The mean age of the sample was 26.41, SD=10.38.

Results: Multiple regression analyses were utilised to examine predictors of psychopathology at group level. For the WS group, increased current health difficulties and sensory processing impairments predicted increased psychiatric disturbance $F(5,28)=8.16$, $p<.0001$, adj $R2=.52$. In PWS, only poorer adaptive ability was influential in predicting increased overall psychiatric disturbance (B-1.41, p=.001), generalised anxiety (B=-0.37, p=.006) and hyperactivity (B=-0.38, p=.003). There were no significant predictors of psychopathology for individuals with FXS.

Conclusion: This study highlights dissociations in the risk factors of psychopathology between the three syndromes. Adaptive ability may contribute to the development and maintenance of psychopathology in PWS, whereas health difficulties and sensory processing may be influential for individuals with WS. Identification of risk factors may be beneficial in assisting diagnosis and informing prevention strategies for psychiatric difficulties.

Keywords: Williams syndrome, Prader-willi syndrome, fragile X syndrome, psychopathology, risk factors.

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TALK 15: The Prevalence and Profile of Anxiety Disorders in Cornelia de Lange and Fragile X Syndromes

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Background: Anxiety is common in neurodevelopmental disorders with particular syndromes at higher risk for specific types; however little is known of how these meet diagnostic clinical criteria. This study investigated the prevalence and profile of anxiety disorders in individuals with Cornelia de Lange syndrome (CdLS) and fragile X syndrome (FXS).

Methods: Caregivers of individuals with CdLS (n=47; 3–53years) and FXS (n=33; 6–48years) completed the Kiddie Schedule of Affective Disorders and Schizophrenia, alongside measures of ability (Vineland Adaptive Behaviour Scale) and autism spectrum disorder (ASD; Social Responsiveness Scale); across which groups were comparable ($p>.05$).

Results: No group differences were found in the number of individuals meeting *threshold* for at least one anxiety disorder (CdLS=55.3%, FXS=42.4%; $p>.05$), but individuals with CdLS were significantly more likely to show comorbidity of disorders (CdLS=23.4% FXS=9.1%; $p<.05$). The most common disorders in CdLS were specific phobias (48.9%), generalised anxiety disorder (21.3%) and selective mutism (16.7%) whereas in FXS these were specific phobias (39.4%) and generalised anxiety disorder (12.1%). An additional 55.3% and 45.5% of individuals with CdLS and FXS scored *subthreshold* for anxiety disorders, with only 19.1% and 33.3% respectively scoring *not present* for any disorder. Associations between anxiety profiles and participant characteristics including age, ability, and ASD characteristics will be described.

Conclusion: Anxiety disorders were prevalent in CdLS and FXS. Interestingly, there were a number of individuals scoring only at *subthreshold* for anxiety disorders but still reporting significant impact on daily functioning. One difficulty was that many anxiety disorders require informants to report on internal thought processes, which is challenging for individuals with low cognitive ability and expressive language skills. This should be evaluated alongside the specific profiles of anxiety disorders and associated participant characteristics in these syndromes, in order to aid the understanding of underlying mechanisms and identification of opportunities for intervention.

Keywords: Anxiety Disorders; Cornelia de Lange syndrome; fragile X syndrome; Phobias; Generalised Anxiety Disorder; Intellectual Disability.

TALK 16: Emotional Dysregulation, Low Mood and Anxiety in Rubinstein-Taybi Syndrome

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Background: Individuals with Rubinstein-Taybi syndrome (RTS) are reported to experience anxiety and mood disorders in adolescence and adulthood. There is increasing evidence that in the general population emotional dysregulation may be a risk marker for the emergence of these difficulties. The aim of this study was to examine the associations between low mood, anxiety and emotional dysregulation in RTS at two time-points (2010 and 2018).

Methods: Parents/carers (N = 48) of children and adults with RTS (mean age: 21.54; range: 6 – 53 years) completed the Mood, Interest and Pleasure Questionnaire (MIPQ) and the Behaviour Rating Inventory of Executive Function (BRIEF-P) in 2010 as part of a large-scale cross-syndrome study. In 2018, these measures were repeated along with the Anxiety and Depression and Mood Scale.

Results: In the cross-sectional analysis, low mood as measured by the MIPQ, was associated with poorer inhibitory control (R = -.43, p =.002) and poorer emotional regulation (R = -.42, p =.002) on the BRIEF-P. Low mood was not associated with ability level. These findings will be discussed along with preliminary findings from the longitudinal study.

Conclusion: The findings provide further support for a link between emotional dysregulation and mental health difficulties, and suggest that emotional dysregulation should be explored further in RTS. Observational and psychophysiological measures of emotional dysregulation in RTS should be pursued to validate these findings.

Keywords: Rubinstein-Taybi syndrome, emotional dysregulation, anxiety, mood.

TALK 17: A Community-Based Parenting Intervention for Parents of Children With a Disability: Comparison of Effectiveness for Children With and Without Autism Spectrum Disorder

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Background: Among children with intellectual disabilities, children with Autism Spectrum Disorder (ASD) have higher rates of behaviour and emotional problems than those without ASD. Parent training programmes, such as Stepping Stones Triple P (SSTP), have been shown to reduce child behaviour and emotional problems. This study aimed to evaluate whether the community-based SSTP programme produced comparable outcomes for children with and without ASD (i.e. whether having ASD moderated the treatment outcome effect).

Methods: A sub-sample of 365 families who took part in the Stepping Stones Triple P (SSTP) programme was analysed, including children with an intellectual or developmental disability aged 2 – 10 years. Parents reported whether their child had been diagnosed with ASD, and completed socio-demographic information and measures assessing child behaviour and emotional problems, and parenting style pre-, post-intervention, and at 12-month follow-up.

Results: Although the children with ASD (n=230) had significantly higher rates of behaviour and emotional problems at all time points compared to the children without ASD (n=135), both groups demonstrated significant decreases in behaviour and emotional problems post treatment. These gains were maintained at 12-month follow-up for overall behaviour and emotional problems, disruptive behaviours, self-absorbed behaviours, and communication disturbance. There was however a small increase in anxiety at 12-month follow-up for children without ASD only. Additionally, there was a continued decrease in social relating problems for the children with ASD, but not for those without ASD. A similar pattern of improvement and maintenance was found for parenting skills (consistency, coercive, positive encouragement) between the parents of children with and without ASD.

Conclusion: Overall, the community-based SSTP program demonstrated a comparable effectiveness in reducing child behaviour and emotional problems, and maintaining the gains during the 12-month follow-up period for children both with and without ASD.

Keywords: ASD, behaviour and emotional problems, parenting skills, treatment.

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TALK 18: Communication in Angelman Syndrome: An Isolated Problem of Speech Production?

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Background: Angelman syndrome (AS) is caused by deletion or alteration of gene UBE3A. Speech is absent for all genetic causes regardless of cognitive ability, however, it is not known if other forms of expressive communication are affected. By examining the communication profile of deletion and non-deletion genetic causes we can ascertain whether: 1) spoken language deficits dissociate from other communicative abilities and 2) if spoken language deficits are unrelated to general cognitive impairment.
Methods: Questionnaire data were collected on receptive and expressive language and gesture use for children with AS (deletion (n = 18) *Mage* = 9.88, *SD* = 4.58; non-deletion (n = 22) *Mage* = 9.33, *SD* = 3.50). Gesture use (including intentionality) and verbal and non-verbal communication were also assessed using behavioural coding (deletion (n = 27) *Mage* = 9.75 *SD* = 3.83; non-deletion (n = 10) *Mage* = 9.75 *SD* = 4.11).
Results: Non-deletion AS evidenced significantly better receptive (p<.001) and expressive language (p=.001) and more gesture use (p<.001) than deletion AS, yet their expressive language was still impaired relative to TD children of similar receptive language abilities (p<.001). There were minimal between group differences in amount of verbalisations (p=.025) but non-deletion AS had a wider range of gestures, more intentional communication and used significantly more symbolic forms of communication (p<.001) than deletion AS.
Conclusion: Spoken language skills dissociate from other communicative abilities in AS. While both groups were characterised by absent speech, gesture use and other non-verbal communication skills were present in both groups and were more evident in the non-deletion sample. Universal absence of speech in AS, even in individuals with relatively good non-verbal communication skills, implicates involvement of UBE3A in speech production. Evidence of intentional communication, despite absent speech, suggests that use of alternative communication aids would be effective in this population.

Keywords: Angelman syndrome, communication, genotype-phenotype, language, gesture use, observational analysis.

TALK 19: Meeting Developmental Milestones in Angelman Syndrome: Wide Age Ranges and Phenotypic Involvement

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Background: Angelman Syndrome (AS) is a rare neurodevelopmental disorder affecting between 1 in 15,000 and 1 in 24,000 individuals. The condition results in severe delays in development and expressive language, and motor impairments. The Global Angelman Syndrome Registry was developed by families to facilitate large scale longitudinal studies to advance research and therapeutics. The current study describes preliminary findings on developmental milestones in individuals with AS.

Methods: 133 parents/carers completed the developmental history section of the registry. 606 children and adults with AS have been registered within the registry. Items enquire about the child/adult's age at which they reached milestones such as sitting, walking, and talking, and their ability in and frequency of performing these activities. 74% of the sample had a chromosome deletion and 21% had a UBE3A mutation, imprinting centre defect (ICD) or paternal uniparental disomy (UPD). The average age of individuals was 10.38 years (range 1.40 to 44.17).

Results: Parents/carers indicated that the individual first sat up between the ages of 4 months and 4 years (mean 15 months), while 9% could not sit. Deletion positive individuals first sat at a later age than those with other diagnoses (Mann Whitney $U = 996.500$, $p < .01$). Individuals with AS crawled between the ages of 6 months and 18 years (mean 22 months), and took their first steps between the ages of 11 months and 7 years (mean 3 years and 4 months). 19.5% and 29% were unable to crawl and walk respectively. Individuals were aged between 6 months and 21 years when they said their first word, although 38% had never spoken. Parents and caregivers of deletion positive individuals reported that the individual sat, crawled, walked or spoke less often and with greater difficulty compared to parents/carers of individuals with other diagnoses ($r = .212$-$.342$).

Conclusion: Findings indicate a wide range of ages in meeting developmental milestones, with a diagnosis of deletion positive associated with greater limitations as reported by parents/carers.

Keywords: Angelman Syndrome, registries, rare diseases, community-based participatory research, developmental milestones.

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TOM OPPÉ DISTINGUISHED LECTURE:

School Non-attendance in Young People With Developmental Disabilities: The Need for Better Recognition.

Emeritus Professor Bruce Tonge

Centre for Developmental Psychiatry & Psychology, Department of Psychiatry,
School of Clinical Sciences at Monash Health, Monash University, Melbourne, Australia.
Centre for Educational Development, Appraisal and Research, University of Warwick, Coventry, UK.

In general, being absent from school for any reason, for 6 or more days a year increases the risk of later numeracy and literacy problems, a range of social and emotional difficulties and economic cost. School non-attendance is prevalent in typically developing students. Preliminary evidence suggests that rates are at least double in young people with developmental disabilities (DD) and treble in those with persistent absenteeism. Little is known about the nature, risks and consequences of non-attendance in children and adolescents with DD. Preliminary data will be presented from the Australian Child to Adult Longitudinal Study (ACAD, Einfeld and Tonge *et al)* indicating school refusal symptoms are prevalent (16%), increase with age, more likely in those with milder ID, and in those with higher levels of emotional and behavioural disturbance. Some syndromes (ASD, Williams, Prader-Willi) had an increased prevalence and others, (Down, Fragile X) a reduced prevalence. In order to study these complex problems based on a proposed typology and bio-ecological theory of school non-attendance, we have developed a school non-attendance checklist (SNACK) now being applied in several studies of children with ASD. The My Say study (N=308) and an on line Warwick University survey of the parents of 488 young people with ASD (NAME) will be reported. These studies suggest that a pattern of interaction of factors accounts for school absenteeism in students with neurodevelopmental problems that might identify at risk students and suggest approaches to management and prevention. Information on the nature of school non-attendance problems associated with specific behavioural phenotype profiles is important in planning management.

Abstracts Provided for NBPSA/ SSBP Educational Day *In order of presentation*

KEYNOTE: Tuberous Sclerosis: Associated Neuropsychiatric Disorders (TAND)

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

Tuberous Sclerosis Complex (TSC) is a multi-system genetic disorder associated with a range of physical manifestations, most prominently in the brain, skin and kidney. Over the last two decades significant progress has been made to identify and treat these manifestations, including through the use of molecularly-targeted treatments using mTOR inhibitors. TSC is, however, also associated with a wide range of behavioural, psychiatric, intellectual, academic, neuropsychological and psychosocial difficulties that are often under-diagnosed and under-treated. Here we present an update on TSC-associated neuropsychiatric disorders, abbreviated as "TAND", to guide screening, diagnosis and treatment in practice. The presentation is aimed at all clinicians involved in the potential assessment and treatment of children, adolescents and adults with TSC and related disorders. We start with a summary of the conceptual approach to TAND, describe the levels of TAND, and present an update about each level of investigation. We conclude with a few examples of current and future TAND research, including the search for natural clusters of TAND, and the potential to treat not only the physical phenotype of TSC but also TAND with mTOR inhibitors.

Keywords: TSC, TAND, behaviour, mental health, autism spectrum disorder, ADHD, anxiety, depression, scholastic difficulties, neuropsychological deficits

KEYNOTE: How cognition-emotion interactions affect risk & protection for mental health diagnoses in children with 22q11.2 deletion syndrome

Professor Tony Simon
UC Davis MIND Institute.
UC Davis Department of Psychiatry & Behavioral Sciences.

In this presentation I will explore the ways in which cognitive impairments, emotional regulation and environmental demands interact to modulate the challenged child's ability to function in real world environments. Using chromosome 22q11.2 deletion syndrome as a case study, I will present our "coper/struggler" hypothesis of adaptive functioning, which is based on the optimum stimulation curve. Using this, I will suggest ways in which the behaviors that frequently lead to mental health or psychiatric diagnoses like Anxiety, ADHD and related arousal based disorders MAY in some cases be better understood in terms of the adaptive responses to mismatches between a child's abilities and the demands they face. Using this model may help to both better understand the circumstances that produce undesirable or inappropriate behaviors and identify potential remedial targets to help reduce challenges and increase quality of life for all involved.

KEYNOTE: Fragile X Syndrome – Understanding Genes and Humanity

Dr Jonathan Cohen
Medical Director, Fragile X Alliance Clinic, Genetic Clinics Australia
Adjunct Senior Research Fellow, CDDHV, Monash University

Fragile X Syndrome (FXS) is the most common known cause of inherited developmental disability and single gene cause of autism spectrum disorders (ASD). Recognizing the neurobiological basis of FXS informs the need to include pharmacological treatment within a multidisciplinary approach to management. Physical features are often absent so diagnosis rests on requesting 'DNA studies for FXS' as this test is not included in the microarray panel used for developmental delay. Diagnosis allows implementation of specific treatment and management strategies that most effectively help mildly to severely affected individuals find the most appropriate place within their environment and our society.

Intellectual disability and learning disorders are usually recognized in childhood, however, families main request is for help in managing behavioural and emotional disorders. These include anxiety disorders, attention deficit hyperactivity disorder (ADHD), ASD, hyperarousal, aggression and self-injurious behavior.

Whilst males with the full mutation may appear more affected, it is important to note that females can also be severely affected. Even those with higher cognitive function can have significant difficulties with anxiety and executive function disorders.

It is also now recognized that carriers with the pre-mutation may present with a range of neuropsychiatric disorders similar to those seen in the full mutation, albeit usually more subtle in nature.

Current and emerging pharmacological treatments can be very effective in ameliorating presenting behavioural problems and are synergistic with educational and allied health strategies.

Due to the dominant inheritance pattern, the treating clinician will often need to diagnose and manage multiple family members. Academic consensus statements recommend all low risk couples in the general community be routinely offered genetic carrier screening, increasingly as part of an expanded carrier screen and preferably in the preconception setting in order to offer the maximum choice of reproductive options.

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KEYNOTE: Case Presentations: Prader Willi, Williams, 22q11 – Understanding Behaviour in a Syndromic Context

Professor Stewart Einfeld

Brain and Mind Centre, University of Sydney

An approach to the management of behaviour problems in children with genetic syndromes will be presented. A focus will be behavioural issues in Prader Willi, Williams and 22q11 syndromes.

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KEYNOTE: State of the Art Genetic Testing in Children with Neurodevelopmental Disorders

Professor David Amor

University of Melbourne Department of Paediatrics and Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, Australia

It is now recognized that genetic factors are the major cause of intellectual disability and autism. The identification of specific genetic causes for intellectual disability is highly valued by families and facilitates prevention, improved clinical care, and the development of novel treatments. The last decade has seen unprecedented improvements in the identification of genetic causes of intellectual disability. This has been driven by the two testing technologies: chromosome microarray and next generation sequencing, and has resulted in a ten-fold increase in the proportion of children in whom a specific genetic cause can be found. In addition, hundreds of previously unrecognised genetic conditions have been identified using this approach, including some that are surprisingly common. This presentation will provide an overview of recent advances in our understanding genetic causes of neurodisability and the application of new genetic testing technologies to provide answers to individual families.

Key words: intellectual disability; autism; genetics; microarray; next generation sequencing;

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Abstracts for Poster Presentation

In Alphabetical Order

POSTER 1: Exploring Autism Symptoms in Individuals With Prader-Willi and Angelman Syndromes

Baker E.K. [1]***, Godler D.E.*** [1]***, Amor D.J.*** [2]***, Bui M.*** [3]***, Rogers C.*** [4]***, Field M.*** [4] ***and Bretherton L.*** [5]

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[5] *Child Neuropsychology, Murdoch Children's Research Institute, Melbourne, Australia.*

Background: Prader-Willi (PWS) and Angelman syndromes (AS) are imprinting disorders that are caused by genetic or epigenetic changes at the same locus on chromosome 15. PWS results from the loss of paternal genes from chromosome 15q11.2-q13 while AS from the absence of the maternal genes in this region. Overexpression of maternally imprinted genes in the 15q11 – 13 region is also a susceptibility factor for autism spectrum disorder (ASD), which is observed in both PWS and AS. This study aimed to explore symptoms of ASD in individuals with PWS and AS.

Methods: Twenty-five individuals with PWS (44% male; 1.5 – 32.2 years) and 19 individuals with AS (52.6% male; 2.8 – 39.7 years) participated in the study. The Autism Diagnostic Observation Schedule-2nd Edition (ADOS-2) was used to assess ASD symptoms. The Mullen Scales of Early Learning was used to assess cognitive functioning in PWS children aged < 3 years and all individuals with AS. For the remaining PWS participants the age appropriate Wechsler intelligence scale was used to assess intellectual functioning.

Results: Compared to the AS group, the PWS group had significantly higher overall (PWS: Md = 6.00; AS: Md = 3.00, p =.006) and social affect (PWS: Md = 5.00; AS: Md = 3.00, p =.002) Calibrated Severity Scores (CSS). The two groups did not differ on repetitive and restricted behaviour (RBB) CSS (p=.416). However, PWS participants were more likely to display sensory seeking behaviours (p =.013), while AS participants were more likely to display hand mannerisms (p=.001).

Conclusion: ASD symptoms, particularly social communication deficits were more common in individuals with PWS compared to individuals with AS. Stereotypies beyond insistence on sameness and compulsive behaviours may be ‹red flags› for ASD in PWS participants, while atypical social interaction may warrant further assessment for ASD in individuals with AS.

Keywords: Prader-Willi Syndrome; Angelman Syndrome; Autism; Intellectual Functioning.

POSTER 2: Clinical Phenotype of Fragile X Patients that are Mosaic for Full Mutation and Normal Size Alleles

Baker E.K. *[1], Arpone M. [1,2], Aliaga S. [1,2], Bretherton L. [3], Bui M. [4], Kraan C. [1,5,6], Santa Maria L. [7], Field M. [8], Amor D.J. [1,6,9] and Godler D.E. [1,6]*

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Background: Fragile X Syndrome (FXS) is caused by a large trinucleotide CGG expansion (>200 repeats), termed full mutation (FM), within the *FMR1* gene located on the X chromosome. FM alleles are associated with epigenetic changes that result in decreased production of *FMR1* mRNA and loss of the *FMR1* protein (FMRP). Up to 41% of those with FXS are described as mosaic. Typical mosaic cases have both FM and pre-mutation (PM: 55 – 200) alleles, while cryptic mosaic cases, that may be missed by standard testing, have a normal size (6 – 44) allele, grey zone (45 – 54) and/or PM alleles together with an FM expansion. To date, no studies have compared clinical and molecular characteristics of cryptic mosaic patients with typical mosaic groups and non-mosaic FM.
Methods: 102 males (68.6% FM) with FXS aged between 1.15 and 43.17 years, recruited from Australia and Chile were included in this study. Participants completed a standardised cognitive assessment and the Autism Diagnostic Observation Schedule-2nd Edition (ADOS-2). Parents/caregivers completed the Aberrant Behavior Checklist-Community (ABC-C).
Results: Typical mosaic participants had higher FSIQ scores (p =.015) and better quality of life (ABC-C utility index; p =.010) compared to FM only participants; while the cryptic mosaic group did not significantly differ for these measures to either the FM or typical mosaic (p >.05) groups. The cryptic mosaic group had significantly lower repetitive and restricted behaviour (RRB) calibrated severity scores (CSS) compared to the FM group (p=.004). The three groups did not differ on overall or social affect CSS.
Conclusion: RRBs were significantly reduced in the cryptic mosaic group compared to both FM and typical mosaic groups. Gaining a better understanding of the clinical presentation in cryptic mosaic patients may lead to earlier diagnosis by providing referring clinicians with key phenotypic information that can be used to make appropriate referrals.

Keywords: Fragile X; Mosaic; Cryptic; Phenotype; Autism; IQ.

POSTER 3: Tailoring a Brief Sleep Intervention for Autism Spectrum Disorder (ASD): A Randomised Controlled Trial

Bellows S.T. [1], *Sciberras E.* [1,2], *Hiscock H.* [3], *Williams K.* [4], *Howlin P.* [5,6], *Papadopoulos N.* [1] *and Rinehart N.* [1]

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Background: Significant sleep problems occur in up to 86% of children with autism spectrum disorders (ASD), but there are few randomised controlled trials of behavioural sleep interventions for this population. This randomised controlled trial will examine the effectiveness of a brief behavioural sleep intervention for primary school aged children with ASD.

Methods: *Participants:* 234 children aged 5 – 13 years with a clinical diagnosis of ASD, without intellectual disability, recruited via paediatricians, community groups and advertisements. Participants will have a moderate or severe sleep problem by parent report and meet diagnostic criteria for chronic insomnia or delayed-sleep phase. *Treatment:* two 50 minute face-to-face sessions and a follow-up phone call with a study clinician at two week intervals. Treatment involves assessment of child sleep problems, discussion of parental goals, psycho-education, and formulation of a behavioural sleep management plan tailored to the child's sleep problems. Strategies are reinforced and modified on review. Children in the treatment as usual (TAU) group continue accessing health care from their paediatrician as they normally would. *Outcome measures:* Child-sleep problems, social-emotional functioning, behaviour, quality of life, academic and cognitive performance, and parental mental health. Parent and teacher questionnaires completed at baseline, 3- and 6-month follow–ups. Child cognitive and academic assessment at 6 months.

Results: Currently 93 children have enrolled in the trial and follow-up data collection has commenced. Based on a pilot study (n=62), we hypothesise that compared with TAU, treatment children will show (1)decreased sleep problem severity, (2)decreased emotional and behavioural problems, (3)decreased social-communicative symptoms, (4)increased cognitive and academic performance, (5)increased quality of life, and (6)decreased parent mental health symptoms.

Conclusion: This trial will provide critical data regarding the treatment of sleep problems in children with ASD. We expect that the brief sleep treatment program will improve sleep in children with ASD, and child and parent outcomes.

Keywords: ASD, autism spectrum disorders, sleep problems, behavioural intervention, sleep intervention, randomised controlled trial.

POSTER 4: Validation of the Developmental and Well-Being Assessment (DAWBA) in a Clinical Population With High-Functioning Autism

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Department of Population, Policy and Practice, Great Ormond Street Institute of Child Health, United Kingdom.

Background: With increasing awareness of Autism Spectrum Disorder (ASD), referrals for assessment continue to rise. This places a large burden on already over-stretched child and adolescent mental health services. The DAWBA, an online interview for parents, may be a useful screening instrument for ASD. It has been validated previously in a non-clinical community sample of twins. Our study aimed to evaluate its predictive validity in a complex clinically referred sample of children with suspected high-functioning autism.

Methods: The sample comprised 136 children (Females = 53; Males = 83) who were referred for a diagnostic assessment at the Social Communication Disorder Clinic (SCDC) at Great Ormond Street Hospital. Parents completed the DAWBA online prior to undergoing a gold standard multi-disciplinary team (MDT) assessment for ASD. This included completing the Developmental, Dimensional and Diagnostic Interview (3di) and the Autism Diagnostic Observation Schedule (ADOS). Two independent clinicians independently rated the DAWBA using DSM-5 diagnostic criteria and compared results to the clinic's MDT diagnoses.

Results: Compared with an MDT assessment, the DAWBA interview possessed good sensitivity (0.90) but poor specificity (0.13). Overall, 64% of cases were accurately assigned as case/non-case. Estimates of positive (0.66) and negative (0.40) predictive validity were influenced by the relatively high prevalence of ASD in the study sample (65%).

Conclusion: The DAWBA online interview has excellent sensitivity in a clinical population of complex neurodevelopmental disorders, containing a high prevalence of ASD. It could be a useful screening instrument for busy child and adolescent mental health or paediatric services, to guide decisions on the prioritisation of new referrals for an MDT assessment. The SCDC provides a national service, offering secondary or tertiary opinions on disputed cases of suspected ASD, limiting the generalisability of these results. Further evaluation is required in community child mental health or paediatric services.

Keywords: Developmental and Well-Being Assessment; Autism Spectrum Disorder; Autism; Validity; Screening; Assessment.

POSTER 5: How Advances in Next Generation Sequencing Affect Our Understanding of Genotype-Phenotype Relationships in Rare Diseases

Ehrhart F. [1,2]***, Bahram Sangani N.*** [1,2]***, Evelo C.T.*** [1,2] ***and Curfs L.M.G.*** [1]

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Given the purpose of the SSBP studying phenotype-genotype relationships, there are some very recent and important developments in this field. We are at the moment realizing that it becomes somewhat old fashioned to look for diagnosis at the patient's phenotype only as new genetic causes (genes and variants) for rare genetic disorders rush in due to new diagnostic methods. Especially whole exome sequencing (WES) is used by now as a standard for diagnosis of idiopathic autism, intellectual disability and suspected genetic disorders. The side effects of this development are that we are getting increasing numbers of human sequencing data, often along with clinical diagnosis or phenotype description which allows to link genotype with phenotype. This development has led in the past years to the discovery of many new genes responsible for diseases. For Rett syndrome, a rare neurological disorder, by WES only in the past few years 69 new genes have been identified which can cause a similar or even identical phenotype. These genes belong to three major functional groups: neurological function, epigenetic imprinting and regulation of protein translation. This practice also led to increasing discussions about the phenotype spectrum of an individual disorder which may overlap with one or more other disorders questioning the definition of diagnosis. The reasons for this phenotype spectrum are suspected in the genetic variant itself, the individual genetic background (epistasis) and/or environmental influences. Consequently, not only our understanding of gene function, the interaction network of genes in human individual but also the definition of diagnosis itself is on a point of change.

Keywords: Rett syndrome, whole exome sequencing, genotype-phenotype.

POSTER 6: Molecular Pathways Involved in Fetal Alcohol Spectrum Disorders – A State of the Art

Ehrhart F. [1,2]***, Roozen S.*** [1,3]***, Verbeek J.*** [4]***, Koek G.*** [1,4]***, Kok G.*** [1,3]***, Van Kranen H.*** [1,5]***, Evelo C.T.*** [1,2] ***and Curfs L.M.G.*** [1,6]

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Background: Although alcohol and its effects on the human body have been studied extensively, little is known about the development of Fetal Alcohol Spectrum Disorders. The teratogenic effects of alcohol (ethanol, EtOH) during pregnancy can cause mild to severe damage to the development of an unborn baby. Nevertheless, the pathways leading from the damaging agent to the broad variety of physiological and psychological symptoms are not yet fully understood.

Methods: In this study, an overview of the literature based on a systematic review approach and additional database derived knowledge will be provided on our current understanding of molecular pathways related to prenatal EtOH exposure. Moreover, potential knowledge gaps will be identified.

Results: The results showed that the basic metabolism of EtOH is already well known: EtOH itself and its first breakdown metabolite Acetaldeyde have toxic effects and oxygen radicals are produced which deploy the metabolism from radical scavengers. When it comes to the influence on the level of gene expression and its regulation the information is more scattered. It seems to be proven that EtOH uptake affects the following oxidative stress related pathways e.g. apoptosis, cytoskeleton and cell adhesion, and DNA damage pathways but also other signaling pathways like SHH, neurotransmitters, retinol and cholesterol homeostasis. These are known pathways which are involved in the development of the central nervous system and its functions.

Conclusion: Less is known about a dose response relationship and possible involved factors. Whether a pathway is triggered or not is at the moment unclear and possibly due to varying experimental design (in animal studies) and lack of reliable biomarkers to assess the individual EtOH uptake (in human studies). Additionally, it becomes clearer that the individual genetic background (epistasis) and environmental influences also play a role. A big potential lies in the use of integrated data analysis using multi omics data to overcome this gap.

Keywords: FAS, FASD, omics data, molecular pathways.

POSTER 7: How FAIR Data Can Improve Research in Rare Genetic Diseases

Ehrhart F. [1,2]***, Capella S.*** [3]***, Rigau M.*** [3]***, Bosio M.*** [3]***, Jacobsen A.*** [4]***, Roos M.*** [4]***, Curfs L.M.G.*** [2] ***and Evelo C.T.*** [1,2]

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Background: Making data FAIR (Findable, Accessible, Interoperable and Re-usable) becomes more and more important in biomedical research. The process of making data FAIR is nevertheless time consuming and requires some knowledge how to do it properly. Despite of this the added value of well curated data can be very high. In a previous study the sources of MECP2 variation data (MECP2 is the disease causing gene in the neurological disorder Rett syndrome), the database size and their FAIRness was assessed, and up and download functionality was investigated for practical use. In this present study, this information was used 1. to create a workflow for integration of genetic variation data from multiple sources and 2. to investigate the gained data.

Methods: We used genetic and phenotypic information from databases which provide linked diagnosis like RettBase, ClinVar, and DECIPHER and databases which provide just the genetic information like LOVD, ExAC, EVS, and EVA. Other sources like dbSNP or Cafe Variome were not used for this study as they did not provide HGVS compatible unique variations (reference SNP identifiers can be linked to more than one allele) or protein changes which cannot be translated back to a unique change in the DNA.

Results: Once the data has been harmonized we were able to create three subsets of data: MECP2 variants which were found in Rett syndrome patients, MECP2 variants which were found in healthy individuals and MECP2 variants without phenotype information. After analysis of the subsets using variant prediction tools we found that the spectrum of predicted versus confirmed pathogenicity of MECP2 is broader than expected, possibly due to other than genetic factors.

Conclusion: For conclusion, providing data in a FAIR way allows to extend data available for research, for comparison and control of experiments. This is especially advantageous when it comes to rare diseases with little numbers of available data.

Keywords: FAIR data, genetic variation, genotype-phenotype, Rett syndrome.

POSTER 8: Sleep Problems and Parenting Stress in Children With Autism Spectrum Disorder With and Without Intellectual Disability

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Background: Behavioural sleep disturbances are common in children with Autism Spectrum Disorder (ASD), impacting on child and family functioning. Anecdotally, children›s sleep disturbances have been associated with increased parenting stress, particularly for parents who already experience high levels of stress, such as parents of children with ASD and parents of children with intellectual disability (ID). Empirical research supports this by suggesting a relationship between child sleep difficulties and parenting stress in families of intellectually-able children with ASD. Literature also suggests that this relationship exists for parents of children with ID who do not have ASD. However, the relationship between child sleep problems and parenting stress is unknown for families of children with ASD who also have an ID (ASD+ID). This research aimed to: 1) compare sleep problems in children with ASD, with and without ID; 2) examine the relationship between child sleep problems and parenting stress in families of children with ASD, with and without ID.

Methods: Participants of this cross-sectional study were parents of 58 children with ASD aged 6 – 13 years (36 ASD+ID, 22 intellectually-able ASD). Parents completed an online survey including the Children›s Sleep Habits Questionnaire and the Parenting Stress Index-Short Form- 4th Edition.

Results: There was a significant relationship between total child sleep problems and total parenting stress for both the ASD+ID and the intellectually-able ASD groups. Child sleep problems were significantly correlated with all parenting stress subscales in the intellectually-able ASD group and all parenting stress subscales except Parental Distress in the ASD+ID group. There were no significant sleep differences found between children with ASD+ID and intellectually-able children with ASD.

Conclusion: Children›s sleep difficulties appear to be experienced similarly across the autism spectrum and have an association with parenting stress. These findings raise important considerations for the implementation of sleep interventions in children with ASD+ID.

Keywords: Autism Spectrum Disorder, Intellectual Disability, sleep difficulties, parenting stress.

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POSTER 9: Young People With Intellectual Disability and Mental Health Needs: Longitudinal Change in Symptoms

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Background: Although behavioural and emotional problems are known to begin in early childhood, we know comparatively less about how these problems evolve over time. Previous work has revealed that overall, high initial levels of behavioural and emotional disturbance decline slowly over time. This paper aimed to examine this change over time in more detail, specifically at the symptom level.

Methods: Behaviour and emotional problems were assessed using the Developmental Behaviour Checklist (DBC). The course of behaviour and emotional problems were followed in a representative population of 589 children and adolescents with intellectual disability, and samples of children with autism, Fragile X, Williams, Down, and Prader Willi syndromes. Participants were followed over 18 years with 5 waves of data collection. Random coefficient modelling was used to examine the change over time for each item on the DBC (symptom level change).

Results: Seventy-three percent of Time 1 participants were followed up at Time 5. At the item level some symptoms decline over time, some remain relatively stable, whilst some increase. Additionally, non-linear change was also found for some items. The profile of changes was found to differ across syndrome groups.

Conclusion: While overall behaviour and emotional problem decreased over time, this trajectory is not straightforward. Whether profiles of increasing behaviour and emotional problems relate to specific types of mental health disorders is an important area for further research. A better understanding of item level change over time in behaviour and emotional problems will facilitate the development of specific interventions to address the public health problem of behavioural and emotional disturbance complicating intellectual disability.

Keywords: behaviour and emotional problems, longitudinal.

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POSTER 10: School Non-Attendance in Children With Autism Spectrum Disorder (ASD)

Gray K.M. [1,2], *Borland R.L.* [1], *Hu N.* [1], *Melvin G.A.* [1,2], *Hastings R.P.* [1,2], *Totsika V.*[1,2,3], *Heyne D.A.* [4] *and Tonge B.J.* [1,2]

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Background: The benefits of school attendance and its corollary, school completion, are broad and persistent, and well established in the general population. Conversely, school non-attendance is shown to have negative associations, being a strong predictor of worse life health, low academic achievement and eventual school dropout. For children with disability, non-attendance rates are 50% higher than their typically developing peers. A number of factors can drive non-attendance, and this study aims to identify rates, predictors and types of non-attendance in a population of children with Autism Spectrum Disorder (ASD).

Methods: Parents of children with disabilities, aged 2 – 10 years in Victoria, Australia were invited to complete a community survey, MySay, and then completed a follow-up survey 2 years later (MySay2). Parents of 308 children with ASD completed both surveys. Parents were asked to provide information on school non-attendance over the past 4 weeks (20 school days), and information on the reasons for non-attendance was obtained using the School Non-Attendance CheckKlist (SNACK).

Results: Children were absent from school for an average of 1.84 days during the past 20 school days. The four most common types of non-attendance were sickness (60%), refusal (21%), being kept home (16%), and medical appointments (16%). Univariate analysis showed a number of factors including financial hardship, child behaviour and emotional problems, and parental adjustment were significantly associated with the number of days of school non-attendance, though multivariate analysis only showed child anxiety to be a significant factor.

Conclusion: Sixty-one percent (61%) of children with ASD had been absent from school for at least one day in the past month, with over 40% missing 10% or more days (chronic absence). Understanding the types of non-attendance and associated factors can help in developing supports for increasing school attendance for children with ASD.

Keywords: Autism Spectrum Disorder, school non-attendance.

POSTER 11: Development of Novel Sensitive Clinical Outcome Measures Based on Gait for Fragile X Mental Retardation-1 Gene-Related Disorders

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Background: This pilot study investigated clinical phenotype and spatiotemporal parameters of gait in 12 children with Fragile X Mental Retardation-1 (*FMR1*) related disorders (67% female; mean age 12.78 years; 50% Fragile X syndrome (FXS), 50% premutation (PM)) and 14 age-matched typically developing controls (36% female; mean age 12.04 years).

Methods: Gait was analysed using inertial sensors during baseline walking and during performance of cognitive and motor-based dual-tasks (i.e., animal naming, finger tapping and balance tasks). Molecular measures included *FMR1* mRNA and DNA methylation of the Fragile X-Related Epigenetic Element 2 (FREE2) region.

Results: Dual-task gait analysis was found to be feasible and well tolerated in most of the individuals with *FMR1*-related disorders, including those with intellectual disability (IQ<70) and features of Autism Spectrum Disorder. The *FMR1* group showed different gait changes during dual-task walking when compared to the control group, with surprising similarities between PM and FXS cases. *FMR1* participants with intellectual disabilities experienced the greatest dual-task interference from the motor finger tapping condition.

Conclusion: Sensitive clinical outcome measures based on gait have the potential to provide assessment of phenotype severity in *FMR1*-related disorders, including the observed variability in intellectual functioning. In contrast to formal testing of intellectual function and/or questionnaire based assessments, this approach utilising wireless sensors is much easier to implement (15 min for assessment), can be performed in patient homes (highly mobile), providing variability in severely affected individuals that cannot be assessed using formal assessments. Together, these characteristics suggest that wireless sensors monitoring cognitive and motor interference to gait have great potential as an improved clinical outcome measure for FXS, and other neurodevelopmental disorders.

POSTER 12: The Role of MicroRNA 137 and MicroRNA 2682 in Autism and Obesity; A Case Report

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Background: MicroRNAs act as key signalling nodes regulating complex biological networks and play important roles in many neurodevelopmental disorders. Deletions involving microRNA 137 host gene (*MIR137HG*) on chromosome 1p21.3 have previously been reported in 13 children with a variable combination of mild dysmorphic features, intellectual disability, autism spectrum disorder and obesity. Reported deletions are 1.1 – 12 Mb large and involve several genes in addition to *MIR137HG*. We report a unique case of a 25 year old female with a de novo 240 Kb deletion that solely affects *MIR137HG*, including the loci for *MIR137* and *MIR2682*.

Methods: The childhood and adult phenotype of the proband has been characterized by neurodevelopmental history, behavioural, somatic, psychiatric, cognitive, metabolic and genetic assessments. The TarBase v.8 and MicroT-CDS databases have been searched to identify target genes for microRNA 137 and microRNA 2682.

Results: No other genetic alteration than the 1p21.3 microdeletion was identified. Birth weight at term was at the 25 percentile and at six weeks age above the 97 percentile. The proband was slightly dysmorphic. She fulfilled diagnostic criteria for mild intellectual disability (F70.0) and childhood autism (F84.0), but no other (neuro) psychiatric disorder. Body mass index was 51.6. We identified 754/ 49 experimentally validated and 1021/1472 predicted targets for microRNA 137 and microRNA 2682 respectively. Several target genes have previously been proposed as susceptibility genes for neurodevelopmental and psychiatric disorders and obesity and are involved in pathways including homeostatic response to hypoxia, modulation of actin cytoskeleton, adipogenic differentiation, cholesterol transport and metabolism, leptin signalling, energy homeostasis and synaptic function and plasticity.

Conclusion: Our unique case highlights the role of microRNA 137 and microRNA 2682 in obesity and neurodevelopmental disorders. We suggest that these microRNAs may be potential targets for adipose tissue engineering and management of obesity in 1p21.3 deletion carriers and in the normal population.

Keywords: MicroRNA 137, MicroRNA 2682, Autism, Obesity, Copy number variation, Intellectual disability.

POSTER 13: Sources of Information Used by Parents of Children With Genetic Syndromes: An Opportunity to Improve Access to Up To Date Information

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Background: Through genomic medicine there have been advances in diagnostic and treatment possibilities for children with rare genetic syndromes. While it is appreciated that parents of these children are seeking up to date information on their child's syndrome and possible interventions, it is not clear which sources they access nor how confident they are in these sources.

Methods: An online survey was distributed to parents of children with rare genetic syndromes, via parent support groups. Parents of 92 children with Angelman (n=45), 22q11 (n=22) and other syndromes (n=24) responded. Parents were asked which sources they use for up-to-date information relating to their child's syndrome, current and future treatment, and how much confidence they have in each source.

Results: Parents most frequently access their Specific Support Groups for information relating to their child's medical condition, current and future interventions. They have good confidence in the information provided by Specific Support Groups. General Support Groups and Social Media were not frequently accessed, nor did parents have good confidence in them. With regards to the medical professionals involved in their child's care, parents accessed their Specialist and General Practitioner less frequently. While parents had good confidence in their Specialists, they had low confidence in General Practitioners.

Conclusion: This reinforces the importance of Specific Support Groups and how they are a vital stakeholder in the family centered approach to the care of a child with a genetic syndrome. Parents are accessing them for information on their child's syndrome and management, thus it is important that Specific Support Groups are provided with up to date evidence based information to distribute. Additionally, it is necessary as researchers and clinicians that colleagues, including General Practitioners, are kept up to date so they can be confident in managing these patients' issues.

Keywords: Genetic Syndromes; Information Sources; Specific Support Groups; Information Confidence.

POSTER 14: Executive Control Performance and Neural Signals May Relate to Psychosis Risk in Youth With 22q11.2 Deletion Syndrome

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Background: Chromosome 22q11.2 deletion syndrome (22q11DS) occurs in ~1:2000 births. Affected individuals experience cognitive impairments, including to executive function (EF). Youth with 22q11DS have a 20- to 30-fold increased risk of developing schizophrenia. Because patients with schizophrenia show impaired EF, performance on EF tasks in youth with 22q11DS may predict psychosis risk.

Methods: Participants were 12 – 18 year-olds with 22q11DS (n = 42) and their typically developing peers (TD; n = 48). Participants completed attention tasks using a flanker-like paradigm that required monitoring either coloured circles or emotional faces. Participants completed inhibition tasks using a Go-NoGo paradigm where they responded to moles, but not vegetables; or to emotional but not calm faces. Electroencephalograms (EEGs) were collected. In the attention tasks, we examined event-related potential (ERP) components indexing capture by (N2pc), and suppression of lateral distractors (PD). In the inhibition tasks, we examined components indexing conflict monitoring (anterior N2). Participants with 22q11DS completed the Structured Interview for Prodromal Syndromes (SIPS).

Results: On the non-emotional attention task participants with 22q11DS were less accurate and generated larger N2pc and smaller PD components than their TD peers. On both inhibition tasks, participants with 22q11DS produced poorer reactive inhibition than their TD peers. On the emotional inhibition task participants with 22q11DS generated larger N2 components than those who were TD.

Conclusion: On an attention task, participants with 22q11DS showed more capture by, and less suppression of distractors. This pattern resembles that seen in patients with schizophrenia. On an inhibition task, participants with 22q11DS showed worse reactive inhibition, despite a larger neural signal indexing conflict monitoring. This suggests that although participants with 22q11DS exerted effort toward conflict monitoring they were unable to produce effective inhibition. Further, ERP components from both tasks correlated with scores from the SIPS, possibly indicating a relationship between neural signals and psychosis risk.

Keywords: 22q11.2 Deletion Syndrome, EEG, ERP, Attention, Inhibition, Executive Function.

POSTER 15: Youth With 22q11.2 Deletion Syndrome are Impaired by Emotional Stimuli in Executive Functioning Tasks

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Background: Chromosome 22q11.2 deletion syndrome (22q) is the most common microdeletion, occurring in more than 1:3000 live births. It is associated with cognitive impairments as well as an increased risk in the development of schizophrenia. Literature on non-syndromic schizophrenia shows impairments in non-emotional executive functioning tasks preceding the onset of psychosis symptoms. Previous studies of participants with 22q have explored executive functioning with non-emotional stimuli. This study assesses the level of impairment youth with 22q experience when faced with emotional stimuli in executive functioning tasks, with the larger goal of finding risk or protective markers for those who do and do not develop severe psychotic symptoms.
Methods: Participants, ranging from 12 – 18 years old, with 22q (n= 46) and who were typically developing (TD) (n= 49) were assessed on tasks with emotional and non-emotional stimuli that evaluated cognitive flexibility and working memory. Tasks included tracking 3, 4, or 6 images of angry or happy faces and shapes, as well as rule switching between non-emotional stimuli in the form of shapes(frequent) or colors (infrequent) and emotional stimuli such as happy, excited, angry, fearful (frequent) and colors (infrequent).
Results: Overall participants with 22q displayed more impairment on tasks with emotional compared to non-emotional stimuli, especially in the cognitive flexibility task, accuracy on negative affect (angry and sad) was worse compared to the positive affect stimuli (happy and excited). Those with 22q also displayed difficulties on all tasks in comparison to their TD peers. Notably, for working memory TD youth performed worse on non-emotional than emotional stimuli, showing the opposite pattern of those with 22q.
Conclusion: Impairment with executive functioning tasks especially in an emotional situation may be an additional marker of psychosis symptoms. Results from this study will be used longitudinally to correlate with psychosis symptom data.

Keywords: 22q11.2DS, Executive Functioning, Working Memory, Cognitive Flexibility, Psychosis.

POSTER 16: Behavioural Phenotypes: Genetic Simplification Only Serves to Illuminate Complexity: A Challenge to Dualism?

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Background: The authors aim to report on the clinical experience and changing role of the developmental neuropsychiatrist in the management of behavioural phenotypes (BP). We shall discuss implications for diagnosis and management and service development.

Methods: To contrast with past experiences, we shall present a number of clinical scenarios and some case examples to illustrate both the common and the rare clinical predicaments that arose in 25 cases seen in a 6 month experience.

Results: These scenarios and cases provide diagnostic, management, medicolegal and ethical learning points. They illustrate some of the complex co-morbidities and aetiologies. New genetics syndromes present new or unique clinical situations, some of which require novel approaches. In the context of such novelty psychiatrists bring a range of integrative skills to diagnosis and formulation to be helpful and insightful. This includes medical/psychiatric knowledge, family, parental and relationship assessment skills and attention to co-morbidity, plus psychopharmacological experience.

Conclusion: These cases, while benefitting from genetic research, still depend on traditional approaches to child and family assessment. BP have become an established part of child neuropsychiatry but has moved from describing a stereotyped view of the main BP to recognising greater individual differences. Some argue that the new Diagnostic and Statistical manual is unreliable and will soon be redundant, to be replaced by a disruptive research approach of the Research Domain of Criteria, based on genetic/biometric data. These cases confirm the value of the current diagnostic system. When child psychiatry services are overwhelmed, more can be gained by mainstreaming a greater awareness of neuropsychiatry in a context of social and family environment.

Keywords: Behavioural phenotype Developmental neuropsychiatry.

POSTER 17: The Establishment of the Global Angelman Syndrome Registry

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Background: Angelman Syndrome (AS) is a rare neurodevelopmental disorder affecting between 1 in 15,000 and 1 in 24,000 individuals. The condition results in severe developmental and expressive language delays, motor impairments, and a unique behavioural phenotype consisting of excessive laughter, smiling and sociability. The Global Angelman Syndrome Registry was initiated in response to a need for large scale longitudinal studies to advance research and therapeutics for this rare syndrome.

Methods: A parent/ caregiver driven process was utilised to develop the Global Angelman Syndrome Registry. The registry consists of 10 modules which cover patient demographics; developmental, diagnostic, medical and surgical history, behaviour and development, epilepsy, medications and interventions, and sleep. In September 2016 the registry was deployed via the Rare Disease Registry Framework (RDRF) developed by the Centre for Comparative Genomics (CCG) at Murdoch University. Parents and caregivers of individuals with Angelman Syndrome were invited by the registry team and syndrome organisations to submit data to the registry via a secure internet connection.

Results: Since its launch, over 600 individuals with AS have been signed up to the registry worldwide: 54% are from North America, 23% are from Europe, 16% are from the Asia Pacific region, 5% are from South America, and 1% are from the Middle East or Africa. The majority of registrants were children: 9% are aged <2 years, 24% are aged 3 – 5 years, 25% are aged 6 – 10 years, 16% are aged 11 – 15 years, and 10% are aged 16 – 20 years. Only 17% are aged over 20 years. Most participants indicated a chromosome deletion (74%), with fewer participants indicating a mutation (12%), paternal uniparental disomy (7.7%) or imprinting defect (UPD; <5%).

Conclusion: Findings indicate a need to target parents and caregivers of older children and adults, and families from non-English speaking backgrounds.

Keywords: Angelman Syndrome, registries, rare diseases, caregivers, parents, community-based participatory research.

SSBP Syndrome Sheets 2018

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

Angelman Syndrome

Alternative names

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

First description

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

Genetic aspects

Angelman syndrome is caused by a disruption of the maternally inherited proportion of chromosome 15q11.2 – 13 (Clayton-Smith & Laan, 2003; Knoll *et al.*, 1989) via four known genetic mechanisms (Jiang *et al.*, 1998). Approximately 70% of cases are caused by a de novo deletion (Knoll *et al.*, 1989). The deletion can be further categorised as a 'Class I' or 'Class II' depending on the amount of information missing (Sahoo *et al.*, 2006), with Class I deletions representing a larger deletion, encompassing Class II. The majority of deletions in Angelman syndrome are Class II, with an estimated prevalence of between 55 and 60% of de novo deletions (Christian *et al.*, 1995). 2 – 7% of cases are caused by uniparental disomy (UPD; Engel, 1993; Prasad & Wagstaff, 1997), where two copies of the paternal chromosome are inherited, 2 – 8% of cases are caused by a mutation in the UBE3A gene (Kishino, Lalande, & Wagstaff, 1997) and 2 – 5% of cases are caused by an imprinting centre defect (ICD; Bürger *et al.*, 1997). Between 5 – 20% (dependent upon sample and extent of molecular investigations) of individuals with the physical and behavioural features of Angelman syndrome show no identifiable abnormalities in the 15q 11 – 13 region (Clayton-Smith & Laan, 2003; Williams, Lossie, & Driscoll, 2001). A few cases have been reported of mosaic imprinting defect, which results in partial methylation of the imprinting centre (see Le Fevre *et al.*, 2017 for case reports). The genetic association between Angelman syndrome and Prader-Willi syndrome has evoked interest in genomic imprinting (see Brown & Consedine, 2004; Haig & Wharton, 2003 for an excellent discussion).

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

Incidence/prevalence

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

Physical phenotype

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

Children and adults are reported to have difficulties with movement and balance (Williams *et al.*, 2006) and ataxic gait thought to be caused by cerebellar dysfunction (Chéron, Servais, Wagstaff, & Dan, 2005). Scoliosis may develop, especially in less mobile patients. Axial hypotonia is present from birth. Limb hypertonia predominating at the lower extremities appears in infancy. Early onset of seizures in Angelman

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

Behavioural aspects

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

Cognitive aspects

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

Genotype x phenotype correlations

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

Comparisons across the deletion classes (Class I and Class II) highlight Class I deletions (larger amount of information missing) as being associated with lower levels of adaptive and cognitive functioning, including expressive language (Sahoo *et al.*, 2006; Varela, Kok, Otto, & Koiffmann, 2004).

Life expectancy

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

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Effie Pearson, Mary Heald and Chris Oliver
(updated August 2017)

Autism Spectrum Disorder

Classification

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

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

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

Associated conditions

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

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

Genetics

The risk of ASD in siblings of probands is significantly increased and there is a high concordance rate in monozygotic twins. Family studies indicate that the "Broader Autism Phenotype" (i.e. having problems related to social, language and/or cognitive functioning) occurs in up to 20% of first-degree family members. Although ASD is highly heritable there is wide genetic heterogeneity, with multiple modes of inheritance including high rates of de novo mutations and a wide range of possible rare and common copy number variations (CNV's; i.e. submicroscopic chromosomal deletions or substitutions). Diverse clinical phenotypes and limited sample sizes add

to the challenges of identifying the specific genes involved and currently only around 10% to 15% of cases of ASD appear to be associated with a known genetic mutation (Bourgeron, 2016; Krishnan, *et al.*, 2016).

More recently, research has begun to focus on the impact of gene-environment interactions and a number of potential environmental risks has been identified (Mandy and Lai, 2016). These include high maternal and paternal age; maternal health factors such as obesity or drugs taken during pregnancy (e.g. thalidomide, SSRI's and Valproate); immune system abnormalities; pre or peri- natal perturbations, and pre-natal exposure to pollutants and pesticides. However, there is no evidence that MMR or other vaccines are a cause of ASD

Prevalence

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

Physical Phenotype

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

Life expectancy/natural history

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

Behavioural and cognitive characteristics

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

Outcome

Longitudinal studies indicate that many individuals, especially those who are more able, show significant improvements in core autism symptoms and behavioural difficulties with age. However, prognosis is affected by many individual and environmental factors, including IQ and severity of social and communication impairments, and the adequacy of educational, occupational and other support systems (Howlin and Magiati, 2017). Studies focusing on quality of life generally indicate that this is poor (Ayres *et al.*, 2017). Mental health problems, especially related to anxiety and depression, often emerge in late adolescence/ early adulthood. Estimated rates of mental health disorders vary widely but are generally between 40%-60% depending on the samples studied (Moss *et al.*, 2015; Russell *et al.*, 2016).

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Patricia Howlin, August 2017,

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CHARGE Syndrome

First Description

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

Genetics/aetiology

In 2004 mutations in the CHD7 gene (chromodomain helicase DNA-binding protein 7), locus 8q12.1, were identified as a primary cause of CHARGE (Vissers, *et al.*). Its genomic structure spans 188 kb and encompasses 38 exons, the first of which is noncoding. The encoded CHD7 protein is 2,997 amino acids in length and contains several domains that are characteristic for its protein family, the chromodomain helicase DNA binding proteins, an ATP-dependent chromatin remodeling protein family. Subsequent research has found a mutation in this gene in 65 – 75% of cases, but in >90% of "typical" CHARGE patients based on clinical diagnosis.

Incidence/prevalence

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

Physical phenotype

The acronym was suggested by Pagon and colleagues (1981) based on common features: C – coloboma of the eye (missing part of iris and/or retina); H – heart defects; A – atresia of the choanae (bony or membranous blocking of nasal passage); R – retardation 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 (i.e., Verloes, 2005). Diagnosis is difficult because there is great variability in presence and severity of the features.

CHARGE has become the most common cause of congenital deaf-blindness (after "other" and "unknown"). Vestibular difficulties are present due to missing or malformed semi-circular canals and otoliths. Swallowing difficulties are common due to cranial nerve dysfunction. Other problems include gastroesophageal reflux, airway difficulties, chronic otitis media, sinusitis, detached retina, scoliosis, chronic constipation with megacolon, and sleep disturbances. Cranial nerve anomalies are common in CHARGE with as many as 92% having symptoms of at least one anomaly. It is speculated that in some cases all 12 cranial nerves might be affected, but the most common are I, V, VII, VIII, and IX/X.

Behavioural and psychiatric characteristics

There is variability in the presence of behavioural difficulties. Behaviour has been described as very goal directed and persistent, socially interested but socially immature, demonstrating high rates of repetitive behaviour and sensation seeking, including problems with self-regulation and transitioning between activities. The behaviours have led to diagnoses of autism, attention deficit/hyperactivity disorder, obsessive-compulsive disorder, and tic disorder. In one study anxiety disorders were the most common psychiatric diagnosis, followed by autism spectrum disorders and attention deficit hyperactivity disorder (Wachtel, Hartshorne, & Dailor, (2007).

Neuropsychological characteristics

There is considerable variability, with some children very developmentally delayed, and others graduating college. Adaptive behaviour tends to be in the low normal range, with little change over four years. Deficits in executive functions have been identified, particularly difficulties with inhibition, shifting focus, and self-monitoring. Due at least in part to sensory impairments, language development and communication may be severely delayed.

Useful websites/associations for more information

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

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Timothy S. Hartshorne, May, 2015

Coffin-LowrySyndrome

The Coffin–Lowry syndrome (CLS) (MIM 303600) is a syndromic form of X-linked 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

No estimate of the prevalence of CLS has been published, but on the basis of the experience of the researchers, a 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. 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 thelips. Retardation of growth and psychomotor development become apparent gradually in the first years of life. Other possible early signs are sensorineural hearing deficit and microcephaly. The age of walking is delayed, and difficulties in ambulating may persist with a clumsy gait.

Female heterozygotes show variable involvement that can range from short stubby digits with normal appearance to quite marked facial dysmorphism. Ventriculomegaly has been observed in several affected males and females.

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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 and psychiatric illness (depression, psychotic behavior, and schizophrenia) have been described in 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).

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André Hanauer, June 2010
Revised Stewart Einfeld, 2015

Coffin Siris

First description and alternative names

The Coffin Siris syndrome was first described by Grange Coffin, MD and Evelyn Siris, MD 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 5thFingernails".

Genetics and molecular biology

Coffin-Siris syndrome is a SWI/SNF complex disorder (Tsurusaki *et al,* 2014). McPherson *et al.* (1997) describes a 1 male to 3 females distribution, but Fleck *et al.* (2001) found the distribution to be 10 males to 8 females. Both autosomal dominant and autosomal recessive inheritance have been suggested by various studies (McPherson *et al.* 1997).

Studies have examined the candidate region for Coffin Siris. 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). Coffin Siris investigations continue.

Incidence/prevalence

70 cases of Coffin Siris syndrome have been reported as of 2008 (Brautbar *et al.* 2008).

Physical features and natural history

Minimal 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. 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

In the past, individuals may have been institutionalized. Few individuals have been described as aggressive or self-injurious while some have been characterized as having happy personalities.

Neuropsychological characteristics

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

Available guidelines for behavioral assessment/ treatment/management

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

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 50,000 live births (Beck & Fenger, 1985), although this is thought to be an underestimate, with more mildly affected individuals increasingly being identified.

Genetics

CdLS is caused by a deletion in the NIP-BL gene on chromosome 5 (locus 5p13) in 20% to 50% of cases (Gillis *et al.*, 2004; Krantz *et al.*, 2004; Miyake *et al.*, 2005; Tonkin *et al.*, 2004). Additional mutations on the SMC3 gene 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 mutations (Deardorff *et al.*, 2012b) 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; Lui & Krantz 2009). It is probable that there are further unidentified mutations relevant to the cause of CdLS.

The NIP-BL 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 NIP-BL 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). 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).

Physical features and natural history

Individuals with CdLS typically have a low birth weight, small stature, upper limb abnormalities (25%) and hirsutism, although those with a milder presentation seem less affected by these problems (Deardorff *et al.* 2007; Kline *et al.* 2007). Distinctive facial features, including: synophrys, long, thick eye lashes, 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. Some of the most commonly occurring problems include: gastro-intestinal disorders, hearing and eye abnormalities, cardiac and genito- urinary problems. Gastro-intestinal disorders are particularly problematic in CdLS.

Little is known about the life expectancy of individuals with CdLS, although recent research studies have included participants aged 40 years and above (Cochran *et al.*, 2015; Moss *et al.*, 2009; Nelson *et al.*, 2013; 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 social reinforcement for some individuals (Arron *et al.*, 2006). There is a notable association between self-injurious behaviour and associated medical conditions, particularly gastrointestinal reflux (Luzanni *et al.*, 2003).

Self-restraint behaviours are common (Hyman *et al.*, 2002) and this has led to suggestions that individuals with CdLS may be at risk for self-injurious behaviour to become difficult to regulate. The increased frequency of compulsive like behaviours within the syndrome such as tidying up and lining up behaviours (Hyman *et al.*, 2002; Moss *et al.* 2009) also indicates that

individuals with CdLS may be at risk for difficulties with behaviour regulation.

An association between CdLS and autism spectrum like characteristics has been consistently reported (Basile *et al.*, 2007; Berney *et al.*, 1999; Bhyuian *et al.*, 2006; Moss *et al.*, 2008; Nakanishi *et al.*, 2012; Oliver *et al.*, 2011; Strivastava *et al.*, 2014). This association with ASD is not solely accounted for by associated intellectual disability (Moss *et al.*, 2008), although the profile of ASD characteristics appears to be different to that of idiopathic ASD (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. These difficulties may become more prominent with age (Goodban, 1993; Nelson *et al.*, 2014; Richards *et al.*, 2009).

There is emerging evidence indicating broad age-related changes in CdLS including increased anxiety, low mood, social withdrawal and challenging behavior (Berney *et al.*, 1999; Cochran *et al.*, 2015; Nelson *et al.*, 2014; Oliver *et al.*, 2011; 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).

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).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).

A recent study by Reid (2010) demonstrated impairments in aspects of executive function including impairment on tasks requiring generativity (verbal fluency), flexibility and inhibition (rule switch) but not working memory. Digit span (backwards) and verbal fluency skills were significantly negatively correlated with chronological age in CdLS but not a contrast group of individuals with DS, indicating increased deficits in these areas with age.

Available guidelines for behavioural assessment/ treatment/management

- Kline AD, Krantz ID, Sommer A, Kliewer M, Jackson LG, FitzPatrick DR, Levin AV, Selicorni A. (2007) *Cornelia de Lange syndrome: Clinical review, diagnostic and scoring systems, and anticipatory guidance.* Am J Med Gen, Part A 143A:1287–1296.
- Moss, J. and Oliver, C. (2012). *Autism in genetic syndromes: implications for assessment and intervention*. Cerebra E-briefing. Cerebra
- Welham, A., Moss, J. and Oliver, C. (2012). *Special Report: Growing up with CdLS: Changes in adolescence and young adulthood. Special Issue Report for the Cornelia de Lange Syndrome Foundation.* March, S1-S16.

Useful websites/associations for more information

- CdLS Foundation UK and Ireland: www.cdls.org.uk
- CdLS World: www.cdlsworld.org
- FIND resources: www.findresources.co.uk
- Oliver C., Moss J., Petty J., Arron K., Sloneem J. & Hall S. (2003). *Self-injurious Behaviour in Cornelia de Lange Syndrome: A Guide for Parents and Carers. Trident Communications Ltd.*: Coventry. – Available from the CdLS Foundation UK and Ireland.
- CdLS Foundation UK and Ireland (2007). *Facing the Challenges: A Guide for Caregivers to People with the Cornelia de Lange Syndrome* – Book and DVD available from the CdLS Foundation UK and Ireland.
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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). Many infants tend to be of low birth weight and low weight usually persists in the first two years of life for both sexes (Marinescu *et al.*, 2000). Feeding difficulties are common and the associated failure to thrive may be the initial clinical presentation. Some infants may require tube feeding, a process which may have to continue for several years. Gastroesophageal reflux is common in CdCS during the first years of life. Other health problems include respiratory tract infections, otitis media and dental problems. Many individuals with CdCS are prone to developing a curvature of the spine (congenital scoliosis) and this can become more apparent with advancing age. Some of the most frequently cited physically defining features of CdCS are facial characteristics including microcephaly, rounded face, widely spaced eyes, downward slanting of palpebral fissures, low set ears, broad nasal ridge and short neck (Dykens *et al.*, 2000; Marinescu *et al.*, 1999). Studies indicate that facial features change over time, specifically, lengthening of the face and coarsening of features (Mainardi *et al.* 2006).

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

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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.

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

Original description was by J. Langdon Down in 1886. Trisomy 21 was first reported in association with Down syndrome (DS) by Jérôme Lejeune and colleagues in 1959.

Incidence/prevalence

About 1 in 800 live born children have DS. The incidence increases with increasing maternal age, being about 1 in 1400 at maternal age 25 and 1 in 30 at maternal age 45.

Genetics

The presence of a complete or partial third copy of human chromosome 21 (Hsa21) is the cause of DS. Partial copy should include all or part of the long arm of Hsa21.This excess of genetic material leads to a dysregulated expression of certain genes. 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, 2014). The nuclear compartments of trisomic cells undergo modifications of the chromatin environment influencing the overall transcriptome, and gene expression dysregulation domains may therefore contribute to some trisomy 21 phenotypes (Letourneau, 2014).

More than 450 genes have been identified on human chromosome 21. The development of new mouse models, either trisomic for different chromosome segments or for individual genes, has helped narrow the focus to those genes likely to be important contributors to the DS phenotype. Of particular interest are the findings relating to 2 genes located within the putative DS critical region of chromosome 21. These are dual-specificity tyrosine-regulated protein kinase 1 (DYRK1A) and DSCR1.

DYRK1A is particularly expressed in the hippocampus, cortex, cerebellum, and heart—regions affected in DS and overexpressed in fetal DS. Transgenic mice that overexpress DYRK1A show learning and memory deficits. Further, DYRK1A phosphorylates tau protein, and this change is known to be important in initiating the cascade of processes leading to amyloid formation in Alzheimer dementia.

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

The origin of supernumerary Hsa21 in free trisomy is in most cases the maternal meiosis. The risk of recurrence (not allowing for maternal age) is low. About 2% of DS results from an unbalanced translocation (material from one chromosome breaking off and "sticking to" another). This often involves chromosomes 21 and 14, and is usually a "one-off" event. In some cases a parent also has a (balanced) translocation (with no overall disruption of genetic material), and the risk of recurrence is high. 21 to 21 translocations also occur. Mosaicism is a term used to describe the presence of two (or more) cell lines within the body. In DS this means one cell line with trisomy 21 and one unaffected cell line. About 3% of DS probably results from mosaicism (many cases may not be diagnosed). The proportion of affected and unaffected cell lines varies, as does the intellectual impairment. Transient myeloproliferative disorder and megakaryoblastic leukemia of DS are associated with mutations in the GATA1 gene in conjunction with trisomy 21.

Physical features

Two types of phenotypes are observed in trisomy 21: those seen in every patient and those that occur only in a fraction of affected individuals. For example, cognitive impairment is present in all patients with DS, so as muscle hypotonia and Alzheimer disease neuropathology after 35 years (Antonarakis,2004). Motor dysfunction is highly prevalent among individuals with DS, who exhibit clumsy sequences of movements, and poor control in programming motor sequences, their timing and force. Motor dysfunction in DS is accompanied by hyporeflexia and reduced muscular strength and tone (Dierrsen 2012) On the contrary, congenital heart defect occurs only in

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~40% and atrioventricular canal in ~16% of patients. Duodenal stenosis/atresia, Hirschsprung disease and acute megakaryocytic leukemia occur 250-, 30- and 300-times more frequently, respectively, in patients with DS than in the general population. In addition, for any given phenotype there is considerable variability (severity) in expression. DS is also associated with an increased incidence of autoimmune disorders, such as autoimmune thyroiditis, primary sclerosing cholangitis, insulin dependent diabetes mellitus, celiac disease and alopecia areata. On the other hand, DS seems be protective against other conditions, such as multiple sclerosis, Crohn disease, neuroblastoma and the development of most solid tumors, which are rarely reported in association with DS.

Most adults with DS are of short stature (70%), with a characteristic facial appearance. The eyes seem to slope upwards and outwards as a result of alterations in the structure of the surrounding tissues. The nose has a wide bridge, and the head an unusual shape ("brachycephaly"). Protruding tongue is present in 45%. 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. People with DS are prone to disorders of the thyroid gland (15% develop hypothyroidism during childhood or adolescence). Ninety percent of all DS syndrome patients have a significant hearing loss, usually of the conductive type. Sight problems (44 – 71%) are common in DS of advanced age, and in a large percentage of the general population.

Obstructive sleep apnea occurs in over half of children with DS aged 2–4years and is related to otolaryngological problems associated with the disorder and to the atlantoccipital instability.

Life expectancy

Life expectancy has improved markedly over the past 50 years, largely as a result of antibiotic treatment of respiratory tract infections. Survival into the 8th decade is unusual but not extraordinary. The presence of an AVSD often leads to heart and lung failure in early adult life. Although changes in blood cells are relatively common, leukaemia is not particularly common (affecting about 1%).

Behavioural characteristics

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

17.6% of individuals with DS aged less than 20 years have a psychiatric disorder, most frequently a disruptive behaviour disorder such as attention deficit hyperactivity disorder (6·1%), conduct/oppositional disorder (5·4%), or aggressive behaviour (6·5%). Twenty five % of adults with DS present a psychiatric disorder, most frequently a major depressive disorder (6·1%) or aggressive behaviour (6·1%).The dual diagnoses of DS and autism has gained much attention; although the association has always been appreciated, recent reports suggest a frequency as high as 7% and great delays in diagnosis. The stereotype of people with DS as happy, placid individuals with a gift for mimicry is not borne out by recent behavioural research. "Stubbornness" and obsessional features seem to be over-represented, and many people with DS react adversely in situations involving conflict.

No significant associations between age and the range or severity of any behavioural and emotional items were found in adult DS subjects without dementia. This suggested a more positive pattern for ageing adults with DS than has been previously described (Makary 2014).

Cognitive characteristics

Cognitive disability is present in all patients with DS. Most children and adults with DS function in the mild or moderate range of intellectual disability. About 10% have a low average-borderline degree of intellectual disability. A minority have a severe or profound cognitive impairment. In DS patients, the average IQ score is around 50, with individual values ranging from 30 to 70 (Rachidi, 2007).

Almost all children with DS have a relatively specific expressive language impairment. Expressive language deficit in syntax is greater than expressive language deficit in the lexicon. Comprehension of words is typically more advanced than nonverbal cognition .Cognition deficits in verbal working-memory and delayed recall has been described.

Cognitive abilities tend to be greater among people whose DS is caused by mosaicism for trisomy 21.

In adults with DS, neuropathological changes typical of Alzheimer's disease usually develop by the fifth decade of life. Adults with DS are much more likely to develop dementia of Alzheimer type than the general population. On post-mortem examination, almost all adults with DS over the age of 35 have the brain changes characteristic of Alzheimer's disease but only about 45% of those over 45 years of age have clinically apparent dementia. The triplication of the amyloid precursor protein gene (APP) is a candidate for causing dementia in DS. However, additional Hsa21 genes may modulate the effects of APP triplication (Dierssen 2012).

Clinical signs and symptoms of Alzheimer's disease are noted in 75% of DS individuals over 60 years of age, and are most frequently seizures (58%), change in personality (46%), focal neurological signs (46%), apathy (36%), and loss of conversational skills (36%). Seizures appear to be associated with rapid cognitive decline in demented individuals with DS. 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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Updated by Annapia Verri, September 2014

Foetal alcohol syndrome/ Alcohol related neurodevelopmental disorder

First description and alternative names

FAS was first observed in Nantes by pediatrician Paul Lemoine in 1968 who described similar dysmorphic facial features and growth delays in 127 infants of pregnant alcohol-drinking mothers. Fetal Alcohol Syndrome (FAS) was coined in Seattle by David Smith and Ken Jones in 1973(1,2).The Institute of Medicine in 1996 delineated Full FAS, Partial FAS, and Alcohol Related Neurodevelopmental Disorder (ARND) based on the presence or absence of facial dysmorphology and /or growth retardation (3). ARND replaced the old term Fetal Alcohol Effect (FAE). FAS Spectrum Disorders, an umbrella term, was introduced by O'Malley & Hagerman in 1998, refined to Fetal Alcohol Spectrum Disorders (FASDs) by Streissguth & o'Malley in 2000 (4,5). In 2013 DSMV proposed a new diagnostic guideline for those with neurodevelopmental disorders associated with prenatal alcohol exposure (NDDPAE 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.

Genetics and molecular biology

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

Incidence/ prevalence

The recognition and incidence for FAS has been shown to be increasing. Original estimates varied from 3 per 1,000 live births in the USA to 40 per 1,000 births in South Africa. More recent studies in Lazio, Italy and Cape Town, South Africa, have suggested much higher rates of 35/1000 to 890/1000 respectively (6,10,13). Methodological issues, genetic differences in the susceptibility to alcohol based on the mother's liver metabolism, as well as differences in population drinking patterns may account for some of the variance(7). As a result, whilst the exact incidence for any one population differs greatly and is unknown the rates are considered potentially higher than previously thought. No documentation of decreased life expectancy exists.

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. 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 recognisable 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

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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. 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 seque3nce and switch separately but not when these two tasks are combined. Working memory deficits tend to be verbal working memory deficits rather than numerical having implication as to how these skills are tested. (3,5,8,9,10,13).

Brain structural abnormalities

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

Brain neurotransmitter and neurophysiological abnormalities

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

Available guidelines for behavioral assessment/ treatment/management strategies

Despite the high prevalence of the disorder, there have been few actual randomised studies of behavioural interventions specific to a FASD population. Those that have been have been small scale. Whilst some benefits are noted much more work is required. A review by Chandresena recently looked at possible strategies including medical, educational and psychological (16).

Useful websites /associations for more information

- www.fasdaware.co.uk
- www.fasdtrust.co.uk
- www.nofas.co.uk
- www.fasd.ie
- www.nofas.com

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Raja Mukharjee, Kieran D O'Malley, May 2015

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 transcription of many proteins important for synaptic plasticity. FMRP regulates the translation of hundreds of proteins many of which are important for synaptic plasticity and are associated with autism. Fragile X syndrome is the most common inherited cause of intellectual disability and the most common single gene cause of autism. Therefore all individuals with intellectual disability or autism should have fragile X DNA testing if the etiology is unknown. In fragile X syndrome there is enhanced metabotropic glutamate receptor 5 (mGluR5) activity leading to enhanced long term depression (LTD). There is also down-regulation of the GABA system and dysregulation of the dopamine system. Targeted treatments have been developed to reverse the neurobiological abnormalities of fragile X syndrome and are currently being studied in patients with fragile X syndrome.

Genetic aspects

There is sex-linked transmission because the FMR1 gene is on the bottom end of the X chromosome (Xq27.3), so males are affected more severely than females. There is an expansion of the CGG repeat in the promotor region of the FMR1 gene through the generations but progression to a full mutation (>200 CGG repeats) only occurs when it passes through a woman to the next generation. Ninety percent of males with a full mutation (>200 CGG repeats) have intellectual disability and the rest have learning and or emotional problems. When the CGG repeat in the promotor region of FMR1 is greater than 200 there is typically methylation of the FMR1 gene. However, those males with fragile X syndrome who are high functioning (IQ>70) are mosaic (some cells with the premutation (55 to 200 repeats) or partially/completely unmethylated so that some FMRP is produced. In females with fragile X syndrome there is one X chromosome that is normal and the second X chromosome with the full mutation. In these females approximately 25% have intellectual disability and an additional 60% have learning difficulties particularly in math, attention and impulsivity in addition to emotional problems. 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.

Carriers have a premutation and are typically unaffected cognitively, although in approximately 10 to 20% intellectual disability or autism can occur. 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 developmental delay at times but more commonly causes emotional difficulties, such as anxiety or depression in about 30 to 40%, primary ovarian insufficiency in 20% and neurological problems in a subgroup of aging male and female carriers. Additional medical problems that can occur in carriers includes hypertension, migraine headaches, insomnia, sleep apnea, hypothyroidism, gastroesophageal reflux, immune mediated problems, chronic fatigue, fibromyalgia and neuropathy. Additional neurological problems include autonomic dysfunction, intention tremor and ataxia, and the combination of these problems is called the fragile X-associated tremor ataxia syndrome (FXTAS). FXTAS occurs in approximately 40% of older male carriers and 8% to 16% of older female carriers. Brain atrophy and white matter disease are seen on MRI in those with FXTAS. The premutation disorders including FXTAS and the fragile X-associated primary ovarian insufficiency (FXPOI) typically do not occur in those with a full mutation because they usually do not have elevated FMR1 mRNA levels. However, a rare individual

with fragile X syndrome who is partially or completely unmethylated who has elevated FMR1 mRNA has been reported with FXTAS. FXTAS has also been reported in a rare individual with a gray zone allele, specifically a CGG repeat in the 45 to 54 range.

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.

Institutionalized individuals with intellectual impairment of unknown origin have rates of fragile X syndrome ranging from 2.5% to 5.9%. The syndrome is the most common inherited cause of learning disability or intellectual impairment. Approximately 2 to 6% of those with autism have fragile X syndrome and it is the most common single gene associated with autism.

Physical

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, 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 20% and recurrent otitis media occurs in the majority in early childhood.

Life expectancy/Natural history

Probably normal except for those who have seizures. Rare cases of sudden death have been reported in childhood or adulthood. Aging studies in individuals with fragile X syndrome have documented a high rate of Parkinsonian symptoms in the 50s and beyond 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. Verbal intelligence 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 and visuospatial skills are common. The rate of intellectual development diminishes with age, particularly after puberty.

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

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severity of autism in females. Hyperactivity is seen in about 80% of boys although attention problems and impulsivity without hyperactivity can be seen especially in girls with the full mutation.

Treatment

Individuals with fragile X syndrome typically respond well to a stimulant medication after 5 years of age. Clonidine or guanfacine have been helpful for hyperarousal and hyperactivity in children under 5yo or older. Selective serotonin reuptake inhibitors (SSRIs) help anxiety and can be used even in those under 5, although activation can be seen in about 20%, requiring a lowering of the dose or discontinuation. Atypical antipsychotics, most notably aripiprazole, when used in low dose helps to stabilize mood, decrease aggression, improve attention, and decrease anxiety. Minocycline is a targeted treatment for fragile X because it lowers matrix metalloproteinase 9 (MMP9) levels and a controlled trial demonstrated efficacy in young children with fragile X syndrome. Arbaclofen, a GABAB agonist has also been shown to benefit patients with fragile X syndrome particularly those with autism or social deficits although a controlled trial in adolescents did not show efficacy. However, limited efficacy is seen in younger children ages 5 to 11 treated with arbaclofen. The metabotropic glutamate receptor 5 (mGluR5) antagonists have not demonstrated efficacy in adolescents or adults with fragile X syndrome in controlled trials. Newer targeted treatments including metadoxine, lovastatin and an IGF1 analogue are currently undergoing trials in adolescents and adults with fragile X syndrome.

Resources

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

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Randi Hagerman MD, August 2015

47,XXY (Klinefelter Syndrome)

First description and alternative names

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

Genetics and molecular biology

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

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

Incidence/prevalence

The prevalence of 47,XXY is the most common sex chromosome disorder, currently estimated to affect approximately 1:650 males. 47,XXY (KS) is an underdiagnosed condition, as only 25% of all cases are diagnosed. Of those diagnosed, less than 10% of cases were diagnosed before puberty (Bojesen & Gravholt, 2007). However, 47,XXY may be prenatally diagnosed through cytogenetic analysis after amniocentesis or chorionic villus sampling. It may also be prenatally detected through noninvasive prenatal testing (NIPT) and then confirmed prenatally or postnatally. After pregnancy, 47,XXY may be diagnosed through a chromosome karyotype also performed by a blood sample or by a chromosomal microarray (CMA) test. A CMA test consists of a blood sample or oral cheek (buccal) swab. Cheek swab is an easy and painless way to detect abnormalities of chromosome numbers to provide a definitive diagnosis.

Physical features and natural history

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

Behavioral and psychiatric characteristics

Individuals with 47,XXY are at increased risk for behavioral problems and psychiatric disorders. Behavioral problems are variable in incidence—although the child with a prenatal diagnosis presents with fewer problems (Ross *et al.*, 2012; Samango-Sprouse *et al.*, 2013; 2015). Additionally, boys receiving early hormonal treatment in infancy or early childhood have fewer problems than the untreated child or the

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child postnatally diagnosed (Samango-Sprouse *et al.*, 2015). School aged children frequently show problems with anxiety and mood dysregulation, self-esteem, and socialization. Socialization problems frequently relate to inhibition and anxiety, and they may become more pronounced during adolescence especially without hormonal treatment. Some of these problems may originate from frustration stemming from a relatively low expressive ability as compared to receptive skills (Simpson *et al.*, 2003; van Rijn *et al.*, 2006). Testosterone replacement therapy may minimize these neurodevelopmental dysfunction (Ross *et al.*, 2014; Samango-Sprouse *et al.*, 2011, 2013, 2015, 2018).

Neuropsychological characteristics

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

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

Available guidelines for behavioral assessments/ treatment/management

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

tonus and androgen deficiency, an active health style is encouraged from infancy through adulthood. Androgen replacement therapy can improve bone density, increase muscle mass and strength, produce more masculine body contour, and decrease body fat. It can produce adequate pubertal maturation with increased body hair, penile enlargement, and male distribution facial and body hair.

Useful websites/associations for more information

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

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Lesch-Nyhan Disease (LND)

Alternative names:
Historically, Lesch-Nyhan syndrome is the designated term for this disease. Lesch-Nyhan Disease (LND) and hypoxanthine-guanine phosphoribosyl transferase (HPRT, HGprt) deficiency are also used to describe this disease. In addition to the classic form of LND, Jinnah and others have characterized two variant forms of the disorder -- these individuals have higher levels of enzyme activity than patients with the classic form and do not have the feature of self-injurious behavior. Elevated levels of uric acid is present is all three types of LND.

First description:
It is interesting that the first description of Lesch-Nyhan Disease may have been in the year 1267. Beck (Euro J of Ped Surg 1991) identified an original description of what may be LND when he uncovered cases of self-injury, gout, and mental retardation in individuals living in a small village in England where St. Thomas, Archbishop of Canterbury, had been killed. The original account, written by Jacobus de Voragine, suggested the disease might somehow be related to the murder of St. Thomas and the "wrath of God". We have come slightly further in our understanding of the disorder since then … and since the first description of the familial nature of the disease by Dr. Nyhan, and his medical student, who published data in 1964 on two brothers with LND in the American Journal of Medicine 36, 561 –570. Nyhan followed up this first article with a second article in 1965, A familial disorder of uric acid metabolism and central nervous system function in J of Pediatrics, 257 – 263. Not only was Nyhan the first to describe the familial nature of the disease, he has devoted his career to the study and care of patients with a variety of metabolic disorders including LND.

In 1959, two physicians, Catel and Schmidt, described what has turned out to be the first variant of the disorder of partial HPRT deficiency (Kelley-Seegmiller syndrome) which, in turn, involves a variable degree of neurological symptoms without the self-injurious behavior of LND. Two variants of classic LND have been further characterized by Dr. Jinnah and colleagues. Seegmiller discovered the enzyme defect in the purine salvage pathway in 1967. Of interest, in 1960, Riley described gout and cerebral palsy in a 3 year old that may be the first classic case of LND in the literature. Hoefnagel *et al,* in 1965, were the first to suggest it was X-linked. In 1983, Wilson and Kelly identified the first specific mutation at the molecular level: a single nucleotide change in the codon for aspartic acid 193 -- GAC for AAC. This discovery has turned out to be one of many, many different nucleotide changes identified in this gene!

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

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

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

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

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X chromosome. Remarkably, over 600 different mutations have been identified in different families (O'Neill and others). The product of the normal gene is the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT) which recycles purines from DNA and RNA. Because it is an X-linked recessive mutation, it ought to occur only in males, but there have been several documented cases in females – thought to be a consequence of events explained by the Lyon Hypothesis. Since the 1960's we have known that because of the lack of HPRT, there is an over-production of uric acid and subsequent uric acid stone formation. (Xanthine stone formation is due to dose specific issues of allopurinol.) Unfortunately, treatment of the elevated serum uric acid with allopurinol does not have an impact on the neurobehavioral manifestations of the disease.

Physical phenotype and the basal ganglia:
Among other deficits, patients with LND have reductions of dopamine in the basal ganglia and it is tempting to think of this disease as a basal ganglia disorder, even though other areas of the brain are involved as well. From the motor disorder standpoint, LND is best described as dystonia superimposed upon hypotonia, although chorea, spasticity and athetosis have been described. During volitional movements, the examiner may believe increased tone is present, yet when the movement is over or when the patient is relaxed, hypotonia is clearly evident. Further, anxiety often confuses the clinical picture, as it does with other aspects of the disorder, especially when the patient is examined by a physician unfamiliar with the patient. The question of the presence of athetosis vs dystonia and the presence of hypotonia vs spasticity is often difficult to distinguish on exam by a physician who is not familiar with the behavioral manifestations of LND. LND presents in the first few months of life as a developmental delay and may be diagnosed initially as cerebral palsy. Individuals with classic LND are generally non-ambulatory. The basal ganglia is known to be involved in the regulation of areas other than the motor circuits, including personality, cognition and emotion. Visser, Bar, and Jinnah have reviewed in depth the involvement of the basal ganglia in LND, and their paper started a frame-shift in our understanding of the neurological aspects of the disease.

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

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

Behavioral aspects:
The behavioral phenotype of Lesch-Nyhan Disease, physical and emotional self-injury, including severe self-mutilation and aggressive behavior, are generally involuntary in nature. The self-injurious behavior is not under the patient's control nor does the patient desire it. These self-destructive behaviors usually begin between ages three and six and often escalate as the patient ages and the patient is more physically able to cause self-injury. The first manifestations of physical self-injury are lip biting, finger biting, and biting of the oral cavity. Modes and patterns of self-injury have been previously described in Robey *et al,* and are often specific to each individual patient and appear consistent over the life-span. Patterns of association involve self injury to or about: 1) external surfaces or 2) oral or biting, usually of the lips and fingers. If a patient tends to injury him or herself using external surfaces, this pattern tends to continue throughout the life-span. If the self-injury involves oral cavity or biting, then this pattern will reoccur throughout the life-span. Forms of self-injury include eye-poking, head banging, fingers in wheelchair spokes, and extension of arms in

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doorways. Emotional self injury, or outwardly directed aggressive behaviors, include hitting, kicking, head-butting, biting others, spitting, swearing, ethnic slurs, inappropriate remarks to the opposite sex, frequently changing opinions, and/or lying.

When oral self- injury is present, removal of the teeth is essential to prevent facial disfigurement. Removal of teeth is often difficult for families (and healthcare providers) to accept, however the teeth, when not removed, can be destructive. Decisions regarding dental extraction must be made with physicians who are expert in the comprehensive care of patients with this disorder (www.Lesch-Nyhan.org; Goodman, *et al.*)

Treatment:

Allopurinol is used to lower the elevated serum uric acid. Historically, levels of the serum uric acid have been kept in a range that minimizes the formation of uric acid stones, yet not too low as to lead to the formation of xanthine stones. Nyhan (personal communication) has suggested that further work needs to be performed to address this clinical issue. Certainly, by lowering serum uric acid with allopurinol, death due to chronic renal failure has become quite rare.

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

The use of medications for treating the behavioral component of this disorder is controversial yet most children and adults with LND are treated with different medications. No medication has been found to reverse the so-called 'Lesch-Nyhan behaviors', either motor or behavioral. Selective ignoring is a methodology that is designed to extinguish self-destructive emotional or physical behavior in the LND patient. It requires the caretaker to ignore such behavior by the LND patient towards said caretaker so that the behavior decreases or ceases. Along with selective ignoring, the use of redirection is also found to be helpful. At times controversial, the use of protective devices is essential, yet often problematic for patients and institutions not familiar with the care of LND patients. Professionals unfamiliar with LND may perceive the use of these protective devices from a traditional paradigm of restraints – which is to say, the use of these devices against a patient's will. When protective devices are requested by the patient -- and used to safeguard the patient from him or herself -- the outcome is an extraordinary feeling of comfort and safety. Not allowing the use of protective devices when requested violates the autonomous rights of the patient. In Lesch-Nyhan Disease self-injury far exceeds that associated with other developmental disabilities, and, of course, is a consequence of the neurotransmitter and cell function abnormalities characterizing the disorder. Although not all individuals with this condition demonstrate severe behavioral manifestations, it is reasonable to say that all benefit from the use of protective devices at some point during their lifetime. It is extremely important to note that the Joint Commission and the US government's CMS requirements both include exceptions to the restraint standards for patients with LND. Issues regarding removal of teeth is addressed above (See exceptions to the CMS standard: 482.13. (e) (6).)

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

Life expectancy:

Life expectancy is a difficult issue to address as the extent of the associated clinical conditions of Lesch-Nyhan Disease has not yet been fully characterized. Fortunately, due to the use of allopurinol, which acts as a substrate for xanthine oxidase, patients with this disorder should no longer die of renal complications. There is a suggestion that some patients may die suddenly in their twenties and thirties possibly as a

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

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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.

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

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

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

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Neurofibromatosis Type 1 (NF1)

Genetics
Autosomal dominant. Gene localised to 17q11.2. The gene product (neurofibromin) is thought to suppress tumour formation by regulating cell division. A high spontaneous mutation rate means that about half of all cases arise in unaffected families.

Incidence/prevalence
About 1 in 2,500 births.

Physical features
Physical manifestations of NF1 include café-au-lait spots, intertriginous freckling, Lisch nodules (i.e. pigmented iris hamartomas or freckling in the iris), neurofibromas (i.e. benign Schwann cell tumors, divided into four types: (1) focal or diffuse cutaneous, (2) subcutaneous (under the skin), (3) spinal, and (4) nodular or diffuse plexiform neurofibromas, which develop from nerves and extend into surrounding structures, and which can transform into malignant tumours), optic pathway gliomas, and distinctive bone lesions (e.g., short stature or dystrophic scoliosis) (Williams *et al.*, 2009). Diagnosis of NF1 is normally made if two of the following physical manifestations are present – six or more café-au-lait spots, two or more neurofibromas, skinfold freckling, two or more Lisch nodules or a family history of NF1 (Ferner, 2007).

Life expectancy
Depends on nature and severity of clinical features.

Brain abnormalities
Magnetic Resonance Imaging studies revealed many different abnormalities in the brains of NF1-patients. These include T2-hyperintensities (of which the nature is not yet known, and which do not seem to have clinical implications), volumetric abnormalities (mainly enlargements of subcortical structures), white matter abnormalities and differences in functional connectivity. The last three may be related to cognitive and social outcomes (Payne *et al.*, 2010; Loitfelder *et al.*, 2015).

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

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

Treatment
Because of the multi-faceted nature of NF1, treatment is generally aimed at specific symptoms. For example, optic glioma are most often treated with chemotherapy (Ardern-Holmes & North, 2011). Trials are underway with bisphosphonate drugs to treat bone abnormalities (Heervä *et al.*, 2014), whilst Simvastatin was, until now, shown to be ineffective in treatment of cognitive impairment (Van der Vaart *et al.*, 2013). Methylphenidate does seem to ameliorate some of the cognitive symptoms associated with NF1. Trials are currently underway with new medication (Lamotrigine) to improve cognitive and social functioning in NF1 with relatively little attention for non-pharmaceutical interventions.

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Stephan Huijbregts 2015

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 mental retardation (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 Cardio-Facio-Cutaneous (CFC) syndrome, Costello syndrome, Neurofibromatosis type 1 (NF1), Noonan syndrome with multiple lentigines (formerly called LEOPARD syndrome), Noonan syndrome-like disorder with loose anagen hair (NSLH), and CBL-associated syndrome. They are grouped into the neurocardiofacialcutaneous syndrome family, or the Ras-opathies (Tartaglia *et al.*, 2011).

In the past, Noonan syndrome has -incorrectly- been referred to as 'Male Turner syndrome', 'Female pseudo-Turner syndrome', 'Turner phenotype with normal karyotype', 'Ullrich-Noonan syndrome' and 'Pterygium Colli Syndrome, included'. Although the NS phenotype has resemblance to the phenotype of (Ullrich-)Turner syndrome, the genotypes differ. Other syndromes with different genotypes but some phenotypical similarities to NS are William's syndrome and Aarskog syndrome (Van der Burgt, 2007).

Genetics and molecular biology

NS may occur on a sporadic basis or in a pattern consistent with autosomal dominant inheritance, with a predominance of maternal transmission.

In approximately 50% of the patients a missense mutation is found in the PTPN11 gene on chromosome 12 (12q24.1). Germline mutations in twelve other genes of the Ras-MAPK pathway have been identified as causative in NS and closely related disorders: SOS1 (about 10% of the cases), RAF1 (5 – 15%), KRAS (<2 – 5%), NRAS (<2 – 5%), BRAF (<2%), SHOC2 (<2%), MAP2K1 (MEK1) (<2%), MAP2K2, CBL (<1%), RIT1 (<1%), A2ML1 (<1%), SPRED1, and HRAS. In about 25% of the patients with a clinical diagnosis of NS, no mutation can be found yet (Pasmant *et al.*, 2009; Tartaglia *et al.*, 2011; Aoki *et al.*, 2013; Vissers *et al.*, 2015).

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 eyes, drooping eyelids, and low-set, posteriorly rotated ears with a thickened helix) and 3) congenital heart defects (pulmonary valve stenosis, hypertrophic cardiomyopathy, atrial septal defect). Some additional features are hematologic and ectodermal anomalies, skeletal anomalies, lymphatic dysplasia, cryptorchidism, and a webbed neck. Neonatal feeding difficulties and failure to thrive are present in the majority of infants with NS. Phenotypical expression is highly variable and often milder in adulthood than in youth. 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; The 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.

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Behavioural characteristics and psychopathology

A distinctive pattern of behavioural characteristics can not be recognised, although there are some indications for an increased risk for behavioural problems in children, characterised by social problems, stubbornness, restlessness, and impulsivity. Traits from the autism spectrum and ADHD symptoms have been reported in children with NS in comparison with their nonaffected siblings (Adviento *et al.*, 2013; Pierpont *et al.*, 2015). Classical psychiatric syndromes have only incidentally been described for NS and mainly concern cases of anxiety disorders, obsessive-compulsive disorders, and mood disorders. In adults, alexithymic traits seem to be present more often, as well as elevated levels of psychological and social distress (Verhoeven *et al.*, 2008; Wingbermühle *et al.*, 2009; 2012a). In comparison with women with Turner syndrome alexithymia and impairments in emotion recognition seem to be less pronounced (Roelofs *et al.*, 2015).

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, weaknesses in memory function (inconclusive results mention problems in working memory, long-term verbal memory and immediate visual memory), mild deficits in selective and sustained attention, and suboptimal planning and organisational skills (Wingbermühle *et al.*, 2009; Alfieri *et al.*, 2011a,b; Pierpont *et al.*, 2010; 2013; 2015). These cognitive impairments may explain learning problems and an increased need for special education.

While extensive cognitive problems seem to be 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 management guidelines

The Noonan Syndrome Guideline Development Group (2010). Noonan Syndrome Clinical Management Guidelines. Dyscerne, University of Manchester.

More information

For information on NS in OMIM, online database of human genes and genetic disorders, see: http://www.ncbi.nlm.nih.gov/omim/163950.

For details on the Noonan syndrome support group, see: www.noonansyndrome.org.

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Renée Roelofs, Ellen Wingbermühle, Willem Verhoeven, Ineke van der Burgt, Jos Egger.

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 (~ 70% of cases) and b) maternal uniparental disomy (mUPD) of chromosome 15 where both chromosomes are derived from the mother (~ 25% of cases). Other rarer causes of PWS include imprinting centre defects 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. Other paternally expressed/ maternally imprinted genes in this region include Necdin, MAGEL2, MKRN3, IPW, PAR-1 and snoRNAs including HBII-85 and HBII-438. 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.

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 althoug 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, usually arising out of frustration or change to a familiar routine, and which can result in extreme aggression; mood swings which do not fulfil criteria for a defined psychiatric disorder; and self-mutilation in the form of skin-picking. Recent 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).

Relative to others with intellectual disability, people with PWS are more likely to exhibit severe problem

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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)

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

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.

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.

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: http://pwsa.co.uk/main.php
- PWS Association USA: http://www.pwsausa.org/
- Online Mendelian Inheritance in Man (OMIM): http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=176270

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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 125,000 live births.

Genetics

RTS is a multiple congenital anomaly syndrome. The first genetic abnormalities identified were breakpoints, mutations and microdeletions within chromosome 16p13.3. Molecular analysis subsequently highlighted a gene located on chromosome 16p13.3 that coded for the cyclic AMP response element binding protein (CBP). In addition to the chromosomal rearrangements of chromosome 16, RTS can also arise from heterozygous point mutations in the CBP gene itself. More recently, the E1A Binding Protein, P300 has also implicated. P300 is located at 22q13.2 and is a homolog of CBP. Both are highly related in structure and function and consequently mutations in p300 can also result RTS. However, genetic markers are only found in around 55% of cases and therefore individuals are typically diagnosed through clinical characteristics.

Physical features

The physical characteristics associated with RTS have been well documented and include broad thumbs and toes, microcephaly, excessive hair growth and dental abnormalities. The classical facial appearance in RTS is also well documented. Descriptions typically include a prominent 'beaked' nose, eyes with downward slanting palpebral fissures, long eyelashes, thick eyebrows, and a small mouth. Feeding and related weight difficulties have been reported in the literature, with descriptions of poor appetite, vomiting and failure to thrive during infancy followed by enhanced appetite and weight gain in adolescence. Other health problems include renal abnormalities, constipation, recurrent upper respiratory infections, undescended testes in males and keloids. Importantly, it has been documented that individuals with RTS may suffer an increased risk of developing cancer. Therefore, attention to early symptoms indicative of tumours is important to ensure early intervention.

Behavioural characteristics

Although still in its infancy, the literature outlining the behavioural phenotype of RTS is growing. Studies have described "stubbornness", sleeping difficulties and a tendency for individuals to be "emotional" and "excitable". The presence of ADHD-type behaviours such as impulsivity and hyperactivity has also been noted. The two most frequently noted characteristics relate to social behaviour and repetitive behaviour. Stereotyped behaviours such as rocking, spinning, and hand flapping, appear to be common. Other repetitive behaviours noted in around three quarters of individuals with RTS include an adherence to routine and an insistence on sameness. Reports have described those with RTS as "overfriendly" and "happy" individuals who " love adult attention" and "know no strangers". Such descriptions have led to the suggestion that individuals with RTS may show superior social competency and social communication skills when compared to those with other causes of ID. In a recent study comparing children with RTS to a matched heterogeneous intellectual disability (HID) group, findings showed that those with RTS showed superior performance on items including acceptance of physical contact, initiating play with other children, and quality of eye contact. In this same study individuals with RTS displayed significantly higher scores than matched HID controls on items assessing the stereotypies 'flaps arms/hands when excited', 'extremely pleased with certain movements/ keeps doing them' and 'makes odd/fast movements with fingers/hands'.

Cognitive characteristics

Intellectual disability (ID) is an associated characteristic of RTS. Although estimates regarding the degree of ID have varied across studies it is thought that most individuals lie within the mild to moderate range. Genetics studies have started to link the molecular abnormalities to cognitive dysfunction in RTS. The CREB binding protein implicated in RTS has been shown to underlie long term memory formation and consequently it has been suggested that ID may be

related to impaired long term memory. Preliminary work assessing social cognition in RTS indicates some 'precursor' social cognitive abilities are intact but there may be subsequent deficits in later developing Theory of Mind. In addition, there is emerging evidence that executive function abilities may be compromised in RTS relative to mental age and that these difficulties may be related to repetitive behaviours observed in the syndrome.

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(updated August, 2014)

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Rett Syndrome (RTT)

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 [1]. 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 [2, 3]. 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-CpG-binding protein 2 gene (MECP2) (OMIM 312750) located at Xq28. MECP2 is a transcriptional repressor that binds methylated DNA and influences many different biological pathways on multiple levels [4]. The link to MECP2 was discovered and reported upon by Amir and colleagues in 1999 [5]. To date, several hundred possible mutations have been identified, each contributing to the specific RTT phenotype and severity of symptoms experienced. 67% of all MECP2 mutations are found in eight hotspots: R106, R133, T158, R168, R255, R270, R294, R306. A number of phenotype-genotype correlation studies indicate that certain mutations may contribute to higher or lower levels of neurologic function and developmental skill [6 – 9]. According to Neul *et al.* [6], for example, data from the US-based Natural History Study suggests that individuals with R133C, R294X, R306C and 3' truncations present with milder symptoms, acquiring more gross motor skills and losing fewer fine motor and expressive language skills. Other (epigenetic) factors are also thought to play a role in determining severity, such as X chromosome inactivation and distribution of the abnormal gene in specific brain regions [10, 11]. However, mutations in MECP2 cannot be identified in all cases (or may be detected when no phenotypic characteristics are present) and the primary diagnosis remains clinical rather than genetic.

Mutations in two other genes FOXG1 and CDKL5 have also been found to be responsible for RTT-like phenotypic presentations; these now fall under a banner of RTT-related disorders.

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 [12, 13], 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 [14], 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 [15]. 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 [16, 17]. Recent retrospective studies have, however, shown that early development does not follow quite as typical a trajectory as supposed [18 – 20].

One of the first noticeable signs is a deceleration in head growth following which individuals with RTT demonstrate a 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

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by Andreas Rett), abnormal gait and an inability to walk; additional features include abnormal breathing and sleep patterns, altered muscle tone, scoliosis, growth retardation and small cold hands and feet [20]. Poorly regulated central autonomic function leads to disturbed cardio-respiratory control with episodes of breath-holding, shallow breathing, hyperventilation and Valsalva breathing. Generalised or focal epilepsy is present in over 50% of individuals. 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 [21]. 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 [22], 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 [23, 24] 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" [25] (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 [26]. 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 [23, 27].

Differential diagnosis

Clinical criteria for the diagnosis of classic RTT and its atypical variants (e.g. Preserved Speech Variant, PSV [28]) were revised in 2010 by members of the Rett Search consortium [25]. Following clinical identification, the diagnosis may be confirmed by genetic analysis.

Historically, individuals with RTT were labelled as having an "autism spectrum disorder" (ASD) [29], 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 [30].

Management

In 2007 Bird and colleagues first demonstrated that the symptoms of RTT could be reversed in mice [31]. Since then much research has been devoted to both the treatment and potential cure of RTT (although this continues to be quite some way off) as well as the development of more functional therapies which address day to day care and seek to enhance the participation and quality of life of individuals living with this rare disorder.

Due to their complex physical and psychological needs individuals with RTT and their families require lifelong access to assessment and intervention from expert multidisciplinary teams [32]. Parent associations can also play a vital role in supporting families [33]. Specialist advice is needed in relation to aspects such as feeding and nutritional, epilepsy and non-epileptic autonomic attacks, movement and posture, and communication. Hippo-, hydro- and music therapy are all felt to be of value as is the introduction of augmentative and alternative communication systems [34 – 36], in particular those which make use of eye gaze/eye-tracking technology as a form of access.

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Available guidelines

In recent years, guidelines have been written for the management of scoliosis [37], growth and nutrition [38], and bone health [39] in RTT. An international consortium led by the Rett Expertise Centre Netherlands is currently funded by a HeART Award from Rettsyndrome.org to develop international guidelines for the assessment, intervention and long-term management of communication in RTT. These guidelines are being developed according to the model utilised by the other guidelines, notably combining available evidence with expert consensus. The final guidelines are expected to be published in 2017.

Useful websites/associations for more information

- http://www.rettsyndrome.org
- http://www.rettsyndrome.eu/association-rse/europe/

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47,XXX (Triple X Syndrome)

First description and alternative names
In 1959, Jacobs *et al.* first described 47,XXX (Triple X syndrome) in an infertile female patient. The term "super female" is considered to be controversial and inaccurate, and the term triplo-X syndrome is outdated. The terms 47,XXX and trisomy X syndrome are generally preferred.

Genetics and molecular biology
47,XXX is a sex chromosome aneuploidy condition in which females have an extra X chromosome. This occurs through a nondisjunction event, where the X chromosome fail to properly separate during cell division either during gametogenesis (trisomic conceptus), or after conception (postzygotic nondisjunction). Mosaicism may also occur, and does so in approximately 10% of cases. Mosaicism can occur in many combinations, such as 46,XX/47,XXX; 47,XXX/48,XXXX; 45,X/47,XXX; 45,X/46,XX/47,XXX. Most of the cases are diagnosed through prenatal diagnostic examinations.

Incidence/prevalence
47,XXX occurs in approximately 1:1000 females, but only 10% of cases are ever diagnosed in their lifetime. 47,XXX may be prenatally diagnosed through cytogenetic analysis after amniocentesis or chorionic villus sampling. It may also be prenatally detected through noninvasive prenatal testing (NIPT) but then must be confirmed. Postnatally, 47,XYY may be diagnosed through a chromosome karyotype analysis performed by a blood sample or by a chromosomal microarray (CMA) test. A CMA test also consists of an oral cheek (buccal) swab or blood sample. The cheek swab is an easy and painless way to detect abnormalities of chromosome numbers to provide a definitive diagnosis.

Physical features and natural history
The majority of cases remain undiagnosed since 47,XXX does not present itself with significant facial dysmorphology of striking physical features. Minor features do characterize this karyotype, including clinodactyly, epicanthal folds, hypertelorism, up-slanting palpebral fissures, overlapping digits, pes planus, and pectus excavatum. Tall stature is common, as most adolescent girls with 47,XXX are at or above the 75th percentile for height with the average head circumference at the 50th percentile or lower. Deficits in motor and coordination appear evident, as girls with 47,XXX are sometimes described as being clumsy. Sexual development in girls with 47,XXX is usually normal, but there have been some cases of ovarian or uterine dysgenesis reported. Fertility does not seem to be an issue in 47,XXX girls, except in cases where fertility is complicated by premature ovarian failure (POF).

Behavioral and psychiatric characteristics
Attention problems, executive dysfunction, and decreased adaptive functioning skills may be common features in girls with 47,XXX. Attention deficit hyperactivity disorder (ADHD) is present in 25 – 35% of cases (Pennington *et al.*, 1980; Bender *et al.*, 1993). Low self-esteem appears to be another common feature (Otter *et al.*, 2010).

Increased rates of anxiety, depression/dysthymia, and adjustment disorders are evident in 47,XXX girls (Bender *et al.*, 1993). Generalized Anxiety in these girls may stem from language weakness that arise from demanding verbal environments that surround school settings and social engagement. In addition, language difficulties may affect social adjustment for these 47,XXX, as they may have difficulties communicating with peers, leading to social avoidance. Mood disorders and psychotic disorders have also been reported in some cases, but the studies are outdated and family histories were not comprehensive (DeLisi *et al.*, 1994; Woodhouse *et al.*, 1973).

Scientific progress through neuroimaging findings
Recent neuroimaging studies have found that girls with 47,XXX possess smaller brain volumes compared to controls with various regions affected (Patwardhan *et al.*, 2002). The affected regions in 47,XXX girls correspond to the phenotypic profile of this

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karyotype: language delay, poor executive function, and heightened anxiety. A thinner cortex found in the lateral temporal lobes explains the language delays, as this region is related to language functions. Frontal lobe abnormalities lead to deficits in executive function (van Rijn & Swaab, 2015). Girls with 47,XXX also possess an increased thickness in the medial temporal lobe in the vicinity of the amygdala, which is a region important for social cognition and linked to anxiety (Lenroot *et al,* 2014).

Neuropsychological characteristics

There is a wide range of cognitive abilities in girls with 47,XXX with full scale IQs ranging within normal limits to very few with intellectual deficits (Bender *et al.*, 1983, 2001). Still, cognitive deficits and learning disabilities are more common in 47,XXX girls when compared to sibling controls. Typically, IQ subscales reveal deficits in verbal IQ and intact or accelerated nonverbal/performance IQ.

Infants and toddlers with 47,XXX are at an increased risk for early developmental delays, especially in speech-language development and motor development related to hypotonia and praxis deficits. Expressive language may be more impaired than receptive language, which is associated with future language-based impairment and motor planning deficits.

Available guidelines for behavioral assessment/treatment/management

A comprehensive neurodevelopmental evaluation is important for newly diagnosed infants and young children, and between 6 – 12 months of age for infants diagnosed in the prenatal period. The assessment should include special emphasis on language, motor, and social development. Early neurodevelopmental intervention, speech therapy, occupational therapy and/or physical therapy should be considered, especially if assessment results show scores within the delayed or borderline range.

For school-age children and adolescents, a multidisciplinary assessment, including evaluation with a child psychologist (for learning disabilities, social/emotional problems, and adaptive functioning assessment), as well as speech/language assessment and occupational therapy assessment, is important in order to identify strengths and weaknesses and to help develop appropriate treatments and behavioral interventions. Common problems including learning disabilities, speech-language disorders (including apraxia of speech), ADHD with predominantly inattentive symptoms, executive dysfunction, anxiety disorders, social difficulties, and other mental health problems should be considered and treated if problematic. Consultation with a clinical geneticist, psychiatrist, or neurologist and psychologist is important in females with trisomy X who have associated ADHD, anxiety, and other mental health problems to discuss possible behavioral and/or medication treatments.

Useful websites/associations for more information

- The Association for X and Y Chromosome Variations (AXYS) https://genetic.org/variations/about-xxx/
- The Dutch Parents' Support Website http://triple-x-syndroom.nl/
- The Focus Foundation http://thefocusfoundation.org/x-y-chromosomal-variations/xxx/
- Genetics Home Reference https://ghr.nlm.nih.gov/condition/triple-x-syndrome
- Genetic and Rare Diseases Information Center https://rarediseases.info.nih.gov/diseases/5672/47-xxx-syndrome
- National Organization for Rare Disorders https://rarediseases.org/rare-diseases/trisomy-x/
- Unique http://www.rarechromo.org/information/Chromosome_X/Triple_X_syndrome%20Trisomy_X%20FTNW.pdf

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Updated: The Focus Foundation, USA, 2017

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 (Kwiatkowski *et al.*, 2010).

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 – 2 protein complex acts as 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 Target Of Rapamycin). TSC mutations causes mTOR overactivation, leading to dysregulation of cell growth, proliferation and various other fundamental neurobiological processes (de Vries, 2010, Kwiatkowski *et al.*, 2010). mTOR inhibitors have been approved by the FDA and EMA for the treatment of SEGA and angiomyolipoma associated with TSC. Clinical trials are underway of neurological and neuropsychiatric features of TSC (Curatolo, Moavero & de Vries, 2015)

Incidence/prevalence
Birth incidence of about 1 in 5,800 (Osborne *et al,* 1991).

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 80% of affected people have a lifetime history of epilepsy. Diagnosis is based on meeting clinical criteria for the disorder (Northrup, Krueger *et al.*, 2013). Mutations are identified in 80 – 90% of individuals with clinically confirmed TSC.
TSC is not an inevitably declining condition and any deterioration in physical, neurocognitive and behavioural profile should be further investigated. Life expectancy is influenced by the degree of physical and neurological involvement. Intractable seizures, brain tumours (SEGAs – subependymal giant cell astrocytomas) and renal failure secondary to angiomyolipomas may be causes of death.

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) has been introduced as a summary 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) TSC is associated with high rates of various disruptive behaviours, sleep problems and self-injurious behaviours. Developmental disorders including autism and 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-related disorders are reported. Psychotic disorders should raise the possibility of seizure-related psychopathology (de Vries *et al.*, 2015; Kwiatkowski *et al.*, 2010).

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Neuropsychological characteristics

Global intellectual abilities show a bimodal distribution in TSC. 30% of individuals with TSC have profound global intellectual disability (IQ equivalent <20) and do not show significant developmental gains over time. The remaining 70% fall on a normal distribution curve, shifted to the left. In clinical practice, more than 50% of individuals with TSC will have global intellectual abilities in the normal range. There are, however, high rates of specific neuropsychological deficits in those with normal global intellectual abilities. Specific deficits are most prominent in attentional, executive and visuo-spatial skills. These specific cognitive deficits may be associated with significant scholastic difficulties and impair functional abilities in daily life (de Vries *et al.*, 2015; Kwiatkowski *et al.*, 2010; Tierney *et al.*, 2011).

Available guidelines for behavioural assessment/ treatment/management

International consensus guidelines were drawn up for the assessment of cognitive and behavioural problems in TSC (de Vries *et al.*, 2005). These were revised and are augmented by the new guidelines on screening and assessment (Krueger, Northrup *et al.*, 2013) and by the TAND Checklist (de Vries *et al.*, 2015; Leclezio *et al.*, 2015)

There are currently no TSC-specific treatments available for the neuropsychiatric manifestations of TSC. Clinicians should therefore use evidence-based interventions as for the general population.

Targeted treatments using mTOR inhibitors are currently in clinical trials for the neurocognitive and neurodevelopmental features of TSC (Curatolo, Moavero & de Vries, 2015), but these are not at present recommended outside clinical trials.

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

Useful websites/associations for more information

- UK user/carer organization
  www.tuberous-sclerosis.org
- USA user/carer organization
  www.tsalliance.org

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Petrus J de Vries, (updated July 2015)

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Turner syndrome

First description

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

Genetics and molecular biology

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

Incidence and prevalence

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

Physical features and natural history

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

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

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

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

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

Behavioural and psychiatric characteristics

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

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

Neuropsychological characteristics

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

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

Available guidelines for behavioural assessment/ treatment/management

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

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

Useful websites/Associations for more information

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

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David H Skuse, 2014

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

First descriptions and alternative names

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

Genetics/aetiology

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

Incidence/prevalence

Generally the prevalence of the syndrome is described to be 1 in 3,000 to 1 in 6,000 live births [e.g., 10, 11]. However, it has been argued that the syndrome is still clinically under-recognised with many older individuals diagnosed when they themselves have children diagnosed with the syndrome [12]. Whilst most people, including many health care professionals, have not heard of 22q11.2DS it is the most common cause of syndromic palatal anomalies and also one of the most common causes of congenital heart defects and developmental delay [12]. It is also likely that the prevalence of the syndrome will rise as mortality decreases and reproductive fitness increases [13, 14]. The syndrome affects individuals of both sexes and of different ethnic background equally [15] although it has been suggested that there are sex differences in the expression of the syndrome [e.g., 16, 17].

Physical characteristics

22q11.2DS is a multisystem disorder including more than 180 characteristics. However, there is a large variability in the expression of the phenotype even amongst members of the same family and characteristics can range from life threatening to very mild [18]. The most common features include congenital heart defects (including conotruncal anomalies), palatal anomalies (including submucous cleft palate and/or velopharyngeal incompetence); immunodeficiency; hypocalcaemia and subtle facial characteristics [9] .

Behavioural characteristics

High levels of internalising symptoms and poor social skills are common amongst children with the syndrome [19]. Children with 22q11.2DS are also at higher risk of developing psychiatric disorders such as attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder, anxiety disorders (generalised anxiety disorder, separation anxiety, and phobias) and, arguably autism spectrum disorders [20]. In late teenage years and early adulthood there are an increased risk of depressive disorders and also a high risk of psychotic disorders including schizophrenia. There are indications in the literature that despite the high prevalence of psychiatric disorders, many individuals with 22q11.2DS are not receiving the appropriate psychiatric care (Young *et al* 2011; Tang *et al* 2014).

Cognitive characteristics

Whilst there is a large variability within the cognitive profile of individuals with the syndrome, cognitive impairments are very common and are associated with learning problems. Intellectual functioning typically range from low average to mild intellectual disability with the majority of individuals having an intellectual ability in the Borderline range [21]. Typically, verbal intellectual functioning decline slightly with increased age but more so in the presence of psychosis [22]. Specific cognitive impairments in executive functioning, memory, working memory, sustained attention, numeracy, visual-spatial processing are common [e.g., 23, 24]. In addition, individuals with the syndrome have been found to have deficits in social cognition including problems in interpreting facial expressions [e.g., 25, 26, 27]

Available guidelines for behavioural assessment/ treatment/management

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

Useful websites/associations for more information

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

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Linda Campbell : June 2016

Williams Syndrome (also known as Williams-Beuren Syndrome)

First descriptions:
The syndrome was first described by Williams, Barrett-Boyes and Lowe (1961) in four patients with supravalvular aortic stenosis (SVAS) in association with intellectual disability and an unusual facial appearance, and by Beuren, Apitz and Harmanz (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. 25 – 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 e.g. hernias and premature ageing of the skin. Several genes are also associated with the intellectual disabilities and cognitive deficits observed in WS, including GTF2I, LIMK1 and CYLN2 (see Skwerer & Tager-Flusberg, 2011, for review) Transmission is autosomal dominant and although most cases are de novo occurrences, some instances of parent to child transmission have been reported (Donnai & Karmiloff-Smith, 2000).

Incidence:
The condition is estimated to occur in 1 per 20,000 individuals although higher rates (1 in 7500) have been reported (see Skwerer & Tager-Flusberg, 2011).

Physical phenotype and natural history:
The condition typically presents in infancy with difficulties in feeding, irritability, constipation and failure to thrive. The principal physical characteristics are well summarised by Donnai and Karmiloff-Smith (2000) and Skwerer and Tager-Flusberg (2011). 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 (Howlin, Elison, Udwin & Stinton, 2010; Porter & Coltheart, 2005). Visuo-spatial skills are often thought to be more severely impaired than language related skills, but, in fact, the cognitive profile of WS consists of a 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, e.g. number skills, planning, problem solving and spatial cognition. In contrast, face processing and some aspects of social cognition are seen as relative strengths. Within the verbal domain, auditory rote memory and receptive vocabulary are viewed as strengths, while spatial language (e.g. using spatial terminology), expressive vocabulary, syntax, semantics and grammatical comprehension are generally delayed (see Martens, Wilson & Reutens, 2008; Skwerer & Tager-Flusberg, 2011,for reviews).

Individuals with WS tend to show characteristic patterns of emotions and behaviours. These include

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positive traits such as friendliness, sociability and empathetic nature (Doyle, Bellugi, Korenberg & Graham, 2004; Fidler *et al.*, 2007) but also a range of emotional and behavioural difficulties including hypersociability, preoccupations and obsessions, generalized anxiety, over sensitivity to noise, attentional problems and impulsivity (Davies, Udwin & Howlin, 1998;Einfeld, Tonge & Rees, 2001; Klein-Tasman & Mervis, 2003). Recent studies of adults have reported relatively high rates of psychiatric disorders (Leyfer *et al,* 2006; Stinton, Elison & Howlin, 2010; Stinton, Tomlinson & Estes, 2012). The most commonly identified mental health problems are anxiety, depression and phobias; bipolar disorder, hypomania and a small number of cases of psychotic disorders have also been reported

Further information

- www.williams-syndrome.org.uk

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Patricia Howlin, 2014

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Wolf-Hirschhorn syndrome

Wolf-Hirschhorn syndrome [WHS] is a congenital malformation first described by Wolf *et al.* and Hirschhorn *et al.* in 1965, independently of one another. It is produced by the loss of genomic material at the telomere of the short arm of chromosome 4.

Genetics and Molecular Biology

The genotype often arises from an unbalanced translocation event (t4;8)(p16;23). Most often, however, the genotype is produced by a de novo mutation. The mechanism(s) which produce the deletion are not known, but recent studies suggest that genes within subtelomeric regions are likely to be involved in deleterious chromosomal rearrangements. Deletion size in WHS varies, is most often telomeric, but may be interstitial. The size of the deletion has been associated with the severity in the phenotype. Of the twelve genes identified by the human genome project between 1.2 and 2.0Mb from the telomere of 4p, five (WHSC1, WHSC2, TACC3, SLBP and HSPX153) are suspected of encoding proteins involved in mRNA processes or transcription. WHSC1 and SLBP are both involved in histone metabolism, and therefore might affect the expression of other genes. Hence, it is possible that some of WHS pathology results from the combined effects of haploinsufficiency in more than one of these genes, and generating significant biological changes in the expression of target genes.

Prevalence and Mortality

The genotype is relatively rare – estimates of its prevalence range from 1:20,000 – 50,000 – and results from a deletion at or near the 4p16.3 locus. Mortality rate in the first two years of life is high [~21%]. However, the median life expectancy for those who survive is greater than age thirty years. Nonetheless, life expectancies are far greater for other microdeletion cases than for WHS.

Physical Features

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

Behavioral and Neuropsychological characteristics

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

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Gene Fisch 2014

47,XYY Syndrome

First description and molecular biology

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

Genetics and molecular biology

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

Incidence/prevalence

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

Physical features and natural history

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

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

Behavioral and psychiatric characteristics

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

Prenatal diagnosis was associated with higher cognitive function and less likelihood of an ASD diagnosis (Ross *et al.*, 2015). Further, expression of NLGN4Y, a gene that may be involved in synaptic

function, is increased in boys with XYY vs. XY controls (Ross *et al.*, 2015).

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

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

Neuropsychological and neurological characteristics

47, XYY syndrome is usually associated with normal to slightly diminished cognitive function as measured with IQ; verbal IQ may be more affected than performance IQ. Many boys require speech therapy in their early years. Reading may be particularly affected. Difficulties with attention and impulse control are frequently reported.

47,XYY syndrome is associated to higher risk for seizures, focal epilepsy, and an electroclinical pattern characterized by focal spike and waves (similar to benign focal epilepsy) has been described in 47,XYY boys (Torniero, 2010).

Neuroimaging

Males with 47,XYY show increased total gray matter (GM) and white matter (WM) volume when compared to 46,XY and 47,XXY males (Bryant, 2012). Increased grey matter may be the result of reduced synaptic pruning, leading to altered synaptic function and perhaps increased seizure risk (Bardsley, 2013).

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

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

Available guidelines of behavioral assessment/ treatment/management

Once 47,XYY has been diagnosed, a comprehensive neurodevelopmental evaluation is important for the management of this syndrome. Occupational and physical therapy may be recommended for infants and young boys who have low muscle tone (hypotonia), and speech therapy may be needed for boys who have speech delay. Behavioral therapy or medication for boys may be prescribed for 47,XYY boys with ADHD and/or behavioral problems. Hormonal therapy may be also recommended to supplement development and growth.

Useful websites/associations for more information

- The Association for X and Y Chromosome Variations (AXYS)
  https://genetic.org/variations/about-xyy/
- The Focus Foundation
  http://thefocusfoundation.org/x-y-chromosomal-variations/xyy/

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- Genetics Home Reference
  https://ghr.nlm.nih.gov/condition/47xyy-syndrome
- Genetic and Rare Diseases (GARD) Information Center
  https://rarediseases.info.nih.gov/diseases/5674/47-xyy-syndrome#ref_9860
- National Organization for Rare Disorders (NORD)
  https://rarediseases.org/rare-diseases/xyy-syndrome/

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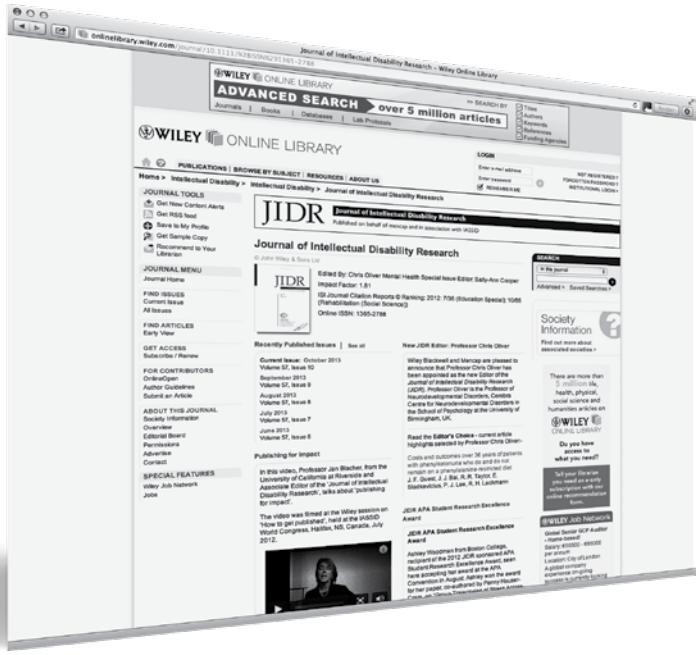

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The 22nd SSBP International Research Symposium

Educational Day 4th September 2019 • Research Symposium 5th – 6th September 2019 • Birmingham, UK

Back to basics in behavioural phenotypes: insights from developing a detailed understanding of behaviour

The International Society for Behavioural Phenotypes will be holding their 22nd Research Symposium in Birmingham, UK, on the 5th and 6th September 2019. The Education Day will be on 4th September prior to the conference. The theme will be: Back to basics in behavioural phenotypes: insights from developing a detailed understanding of behaviour.

Historically, Birmingham was coined the workshop of the world due to its vibrant industrial history. Today Birmingham boasts huge diversity of cultures, cuisines, festivals and heritage attractions. And just a short way from the bright lights of the city are some of the most interesting and idyllic areas that England has to offer.

Registration and abstract submission open: 11th March 2019

Deadline for online abstract submission: 22nd April 2019

Deadline for discounted early bird registration: 26th July 2019

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The 22nd SSBP International Research Symposium

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