22nd SSBP International Research Symposium

Back to Basics in Behavioural Phenotypes: Insights from Developing a Detailed Understanding of Behaviour

Programme Book

4th – 6th September 2019 • Birmingham, UK

Save the date!

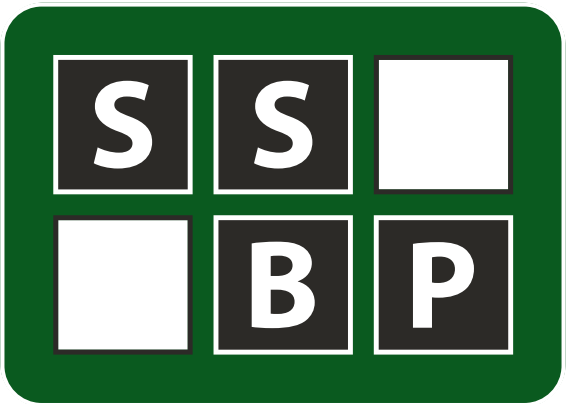
23rd SSBP International Research Symposium will be held in Oslo, Norway in September 2020

Abstract submission opens: 1st April 2020
Registration opens: 1st May 2020
Deadline for online abstract submission: 22nd May 2020
Deadline for discounted early bird registration: 31st July 2020

Educational Day: 10th September 2020
Research Symposium: 11th – 12th September 2020

Join us in Oslo, Norway for our 23rd Research symposium, the theme will be *Developmental disorders and behavioural phenotypes across the lifespan*

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



The Society for the Study of Behavioural Phenotypes

4th– 6th September 2019

The 22nd SSBP International Research Symposium

Back to Basics in Behavioural Phenotypes: Insights from Developing a Detailed Understanding of Behaviour

Birmingham, UK

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Welcome from the Conference Organisers

We are delighted to welcome you to the 22nd Society for the Study of Behavioural Phenotypes International Research Symposium and Education day, held in Birmingham.

Birmingham is the UK's second largest city, famous for its many locks and canals, with the first canal opening in 1979. Birmingham has always been a city of innovation, boasting the development of the X-ray scanner in 1986 and the mass spectrometer in 1919. In is also worthy of note that Birmingham pioneers led the way in making our conference possible, by developing the first photocopier, computer, microphone, camera, stapler and a machine to mass-produce the steel-nib pens at a time when most people relied on quills!

The theme of this year's conference is **Back to basics in behavioural phenotypes: Insights from developing a detailed understanding of behaviour.** This theme cuts across a broad range of topics that will be discussed, from physical health to mental health, from medical to behavioural interventions and from sleep to social cognition. We are very excited by the diversity of keynote speakers that will include issues and approaches relatively rarely addressed in the context of behavioural phenotypes, such as participatory research, computational modelling and family functioning. Ultimately, the research presented will demonstrate the advantages of developing a detailed understanding of behaviour. Whilst at the same time highlighting the associated challenges and how these relate to available and developing methodological approaches. The aim of the conference is to give space to discuss the key methodological approaches that are available to scientists working within the field, and to think together about how to tailor these approaches to ensure excellent scientific rigour and the best outcomes for people with neurodevelopmental conditions. It also provides an opportunity for junior and senior researchers to come together to inspire new ideas and collaboration.

We are also proud that this year's SSBPs conference brings a global perspective to behavioural phenotype research and enthusiastically welcome Cristiane Silvestre de Paula from São Paulo who will be speaking about service use linked to neurodevelopmental disorders in Brazil and five other Latin American countries.

We hope you enjoy your time at SSBP Birmingham.

Dr Jane Waite and Dr Kate Woodcock
Conference Coordinators

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Birmingham Conference Organisers

Dr Jane Waite

Dr Jane Waite is a Lecturer and Clinical Psychologist at Aston University. Jane completed her PhD in the behavioural phenotype of Rubinstein-Taybi syndrome, and then continued her research into rare genetic syndromes including Cornelia de Lange, Williams, Kleefstra, Lowe and Biedl Bardet syndromes. Jane has also worked extensively on online resources (Further Inform Neurogenetic Disorders (FIND); www.findresources.co.uk) with the aim of improving knowledge exchange between families and professionals. Jane's current research focuses on factors that influence mental health outcomes across and within genetic disorders, with a specific focus on low mood, anxiety and temper outbursts.

Dr Kate Woodcock

I am a Senior Lecturer at the Centre for Applied Psychology in the School of Psychology at the University of Birmingham. My research focuses on young people who face behavioural and emotional difficulties, examining factors that come together to precipitate these. My team applies this knowledge to the development of intervention strategies. For example, caregiver led behavioural support, cognitive training, and early intervention. Several lines of our work include a focus on individuals with genetic syndromes (www.katewoodcock.com). I gained my PhD from the University of Birmingham in 2008. Two years of my Postdoctoral Research were at Peking University. I held a lectureship at the School of Psychology, Queen's University Belfast until 2017.

Sponsors

We are very grateful to the following organisations for their sponsorship of the 2019 SSBP Conference.

Scientific Committee

Professor Louise Gallagher
Professor Child & Adolescent Psychiatry,
School of Medicine, Trinity College Dublin, Ireland

Professor Andre Strydom
Professor of Intellectual Disabilities,
Department of Forensic and Neurodevelopmental Sciences, King's College London, UK

Dr Jane Waite
Lecturer in Psychology,
School of Life and Health Sciences, Aston University, UK

Dr Kate Woodcock
Senior lecturer,
Centre of Applied Psychology, School of Psychology, University of Birmingham, UK

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 Petrus* ***de Vries*** (South Africa) (petrus.devries@uct.ac.za)
	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

Africa – *Petrus* ***de Vries*** *(Cape Town)* (petrus.devries@uct.ac.za)
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
2019	Birmingham, UK	22nd International

Forthcoming Meetings of the SSBP

2020	Oslo, Norway	23rd 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

2019	Louise Gallagher
2018	Bruce Tonge
2017	James Harris
2016	André Strydom
2015	Michael Rutter
2014	Stewart Einfeld
2013	Patricia Howlin
2012	Chris Oliver
2011	Tony Holland
2010	Randi Hagerman
2009	Alcino Silva
2008	Hans-Christoph Steinhausen
2007	Petrus J de Vries

2019 Tom Oppé Distinguished Lecturer: Professor Louise Gallagher

MB BCh BAO MRCPsych PhD FTCD

Professor Louise Gallagher, MB BCh BAO MRCPsych PhD FTCD, is Chair of Child and Adolescent Psychiatry Trinity College Dublin (TCD), Director of Research in the School of Medicine, TCD and a Consultant Child and Adolescent Psychiatrist in the Irish health service.

She trained in Psychiatry in Dublin, Ireland in St. Patrick's Hospital, Dublin and she specialised in Child and Adolescent Psychiatry. She was a Consultant Child and Adolescent Psychiatrist in Community Child and Adolescent Psychiatry Services (CAMHS) until her appointment as Chair and Professor of Child Psychiatry in 2011.

She began her research career as a Wellcome Trust Mental Health Training Fellow in 1999. She was awarded her PhD in Psychiatric Genetics in 2004. She specialised in genetic risk factors for autism and study both common and rare genetic risk factors for autism. She has been part of many major international research consortia involved in autism genomics and neuroimaging and has contributed to papers in high level journals such as Nature, Science, Nature Genetics and has raised significant funds for her research through national, European and international grants. Her group has expertise in genotype-phenotype analyses and deep phenotyping approaches including neuroimaging, EEG, cognitive and behavioural phenotyping, neuroimaging and EEG. The work in her group has contributed to the understanding of genetic causes of autism, particularly understanding the relationships between genetic risks, endophenotypes and symptoms ultimately to provide insights into key molecular processes associated with ASD.

As a clinician in the health service she currently runs a service that is specialised in the diagnosis and treatment of comorbid mental illness in autism and providing tertiary opinions on complex behaviour in the context of neurodevelopmental disorders.

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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 as President of the SSBP in 2014.

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

2019	Jeanne Wolstencroft
2016	Shruti Garg
2015	Supriya Malik
2014	Hayley Crawford
2013	Mary Heald
2012	Sheena Grant
2011	Leah Bull
2010	Debbie Allen

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2018 Pat Howlin Lecturer: Jeanne Wolstencroft

Jeanne Wolstencroft is a PhD student intent on pursuing a career in translational psychology. After studying a BSc in Neuroscience, she worked for an online start-up the arts sector. She returned to academia to complete an MSc in Psychology, after which she joined the Great Ormond Street UCL Institute of Child Health to work on the national IMAGINE ID study (Intellectual Disability and Mental Health: Assessing the Genomic Impact on Neurodevelopment). Her PhD research is focused on the link between genetics and mental health, with a special interest in psychological interventions in sex chromosome aneuploidy patients (such as Turner Syndrome). As a post-doc Jeanne aims to adapt evidence-based psychological interventions for online delivery to help manage complex neurodevelopmental disorders.

Twitter: @JeanneWols

Petrus de Vries and the Leclezio-de Vries Lecture

Petrus J de Vries

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

The Leclezio-de Vries Lecture:

Area of Research:

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

Eligibility of applicants:

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

Award Procedure:

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

The award will be judged by the Organising Committee of each Research Symposium who will make a recommendation to the SSBP Executive Committee at least 1 month prior to the SSBP Research Symposium. Once approved by the SSBP Executive, the successful candidate will be invited to present the Lecture. The award winner will receive free registration for the current SSBP Research Symposium along with a prize of £100 (or equivalent) and an award certificate - both of which will be presented to the winner during the SSBP Research symposium.

The Leclezio-de Vries Lecturers

2019	Ms Siobhan Blackwell

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2019 Leclezio-de Vries Lecturer: Ms Siobhán Blackwell

Siobhán is a Research Associate with the Kate Woodcock Research Group, under Dr Kate Woodcock. She is responsible for coordinating the 'Flexible Scheduling' Project. This project is a feasibility and acceptability study which aims to develop an intervention to prevent the development of disabling emotional and behavioural responses to change in groups considered at-risk (autism, Prader-Willi and fragile-X syndromes).

Siobhán completed her Masters in Psychological Science and her undergraduate degree in psychology at University College Dublin, Ireland. Since graduating in 2014, Siobhán has worked in research across various Higher Education Institutions, both in Ireland and England. Her core interests are in developmental psychology. Prior to moving to the UK, Siobhán held the position of Assistant Head Teacher in an early intervention centre for children with autism, as well as a teaching post on two undergraduate modules (Human Development and Psychological Assessment) for the Irish College of Humanities and Applied Sciences.

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Venues

Aston University
Birmingham

1 Educational Day (4th September)

The Educational Day will be held at:
Aston University Main Building, Sumpner Lecture Theatre (Room MB651)

2 Conference Reception (4th September)

The Conference Reception will be held at:
The Library of Birmingham, Centenary Square, Broad St, Birmingham B1 2ND

3 Research Symposium (5th-6th September)

The Research Symposium will be held at:
Conference Aston – Conference Centre & Hotel, Aston Street, Aston University Campus, Birmingham B4 7ET

Directions:
Conference Aston boasts an exceptional location on the Aston University campus, benefitting from extensive transport links.
Rail travel
New Street, Snow Hill and Moor Street train stations are all within 10 – 15 minutes walk of the venue or a 5 minute taxi journey. Please visit www.thetrainline.com for details of times and tickets.

On foot from the stations: Interactive Google walking maps from New Street and Snow Hill train stations, available for download from www.conferenceaston.co.uk/WalkWithGoogle
Bus routes A number of bus services operate to the University campus throughout the day. For further information, please visit www.nxbus.co.uk/west-midlands where a route planner to the Aston University campus is available.
Taxi drop off points All of the venues have taxi drop off points. Be sure to say to your driver that they should go to the Aston University campus. The central drop off point is a minute's walk to the conference centres and hotel.

4 Conference Dinner (5th September)

The Conference Dinner will be held at the Birmingham Botanic Gardens

Birmingham Botanic Gardens, Westbourne Road, Edgbaston, Birmingham, West Midlands B15 3TR

Directions:
The Gardens can be reached as follows:
Buses: 23, 24, 1, X8, 9, X10, 12, 12A, 13, 13A, 13B, X21 and 126 all stop outside, or very close to, the Gardens.
Trains: From Five Ways Station – 20 minutes walk. From Birmingham New Street Station – buses or taxi (approx. 20 minutes).
By Car: Follow signs for Edgbaston then brown tourist signs to Botanical Gardens.

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For a full visitor map of central Birmingham go to: **VisitBirmingham.com**

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Keynote Speaker Profiles:

(in order of presentation)

Deborah Fidler

Dr. Debbie Fidler is a Professor in the Department of Human Development and Family Studies at Colorado State University. Her research expertise is in the area of early atypical development, with a focus on the emerging behavioral phenotype in Down syndrome during early childhood. Dr. Fidler served as Editor of the American Journal on Intellectual and Developmental Disabilities (AJIDD) from 2014 – 2018 and she currently serves as Co-Editor of the International Review of Research in Developmental Disabilities. The overarching goals of her program of research include characterizing phenotypic profiles in specific neurogenetic syndromes, identifying potential targets for treatment and intervention, and developing innovative intervention approaches to address areas of developmental vulnerability.

Louise Gallagher

Professor Louise Gallagher, MB BCh BAO MRCPsych PhD FTCD, is Chair of Child and Adolescent Psychiatry Trinity College Dublin (TCD), Director of Research in the School of Medicine, TCD and a Consultant Child and Adolescent Psychiatrist in the Irish health service.

She trained in Psychiatry in Dublin, Ireland in St. Patrick's Hospital, Dublin and she specialised in Child and Adolescent Psychiatry. She was a Consultant Child and Adolescent Psychiatrist in Community Child and Adolescent Psychiatry Services (CAMHS) until her appointment as Chair and Professor of Child Psychiatry in 2011.

She began her research career as a Wellcome Trust Mental Health Training Fellow in 1999. She was awarded her PhD in Psychiatric Genetics in 2004. She specialised in genetic risk factors for autism and study both common and rare genetic risk factors for autism. She has been part of many major international research consortia involved in autism genomics and neuroimaging and has contributed to papers in high level journals such as Nature, Science, Nature Genetics and has raised significant funds for her research through national, European and international grants. Her group has expertise in genotype-phenotype analyses and deep phenotyping approaches including neuroimaging, EEG, cognitive and behavioural phenotyping, neuroimaging and EEG. The work in her group has contributed to the understanding of genetic causes of autism, particularly understanding the relationships between genetic risks, endophenotypes and symptoms ultimately to provide insights into key molecular processes associated with ASD.

As a clinician in the health service she currently runs a service that is specialised in the diagnosis and treatment of comorbid mental illness in autism and providing tertiary opinions on complex behaviour in the context of neurodevelopmental disorders.

Richard Hastings

Richard Hastings is a Professor of Psychology and Education in the Centre for Educational Development Appraisal and Research at the University of Warwick, and the Cerebra Chair of Family Research. His research team study the psychological difficulties (including mental health problems and behaviours that challenge) of children and adults with intellectual disabilities, and interventions and services for family and paid carers who support these children and adults.

Andreas Meyer-Lindenberg

Prof. Meyer-Lindenberg is Director of the Central Institute of Mental Health and Head of the Executive Board, as well as the Medical Director of the Department of Psychiatry and Psychotherapy at the Institute, based in Mannheim, Germany, and Professor and Chairman of Psychiatry and Psychotherapy at the University of Heidelberg in Heidelberg, Germany. He is board certified in psychiatry, psychotherapy, and neurology. Before coming to Mannheim in 2007, he spent ten years as a scientist at the National Institutes of Mental Health, Bethesda, USA.

Prof. Meyer-Lindenberg is the author of more than 300 peer-reviewed articles and book chapters in journals such as Nature, Science, Nature Neuroscience, Nature Medicine, Nature Reviews Neuroscience, Nature Genetics, Neuron, PNAS, and others. He is has been continuously named as one of the most highly cited scientists in the world (www.isihighlycited.com) He is the Editor-in-Chief of the European Journal of Neuropsychopharmacology, associate editor of Science Advances and on the editorial board of a number of other journals such as Schizophrenia Bulletin, European Neuropsychopharmacology, Psychiatry Research: Neuroimaging, and Neuroimage.

His research interests focus on the development of novel treatments for severe psychiatric disorders, especially schizophrenia, through an application of multimodal neuroimaging, genetics and enviromics to characterize brain circuits underlying the risk for mental illness and cognitive dysfunction.

In recognition of his research, Prof. Meyer-Lindenberg has received awards throughout his career, including: Bristol-Myers-Squibb Young Investigator Award (1998), NIH Award for Excellence in Biomedical Research (1999,2000,2001), NARSAD Young Investigator Award (2000), Department of Health and Human Services Secretary's Award for Distinguished Service (2006), Roche/Nature Medicine Award for Translational Neuroscience (2006), the Joel Elkes International Award for Clinical Research from the American College of Neuropsychopharmacology (2006), A.E. Bennett Award of the Society for Biological Psychiatry (2007), NARSAD Distinguished Investigator Award (2009), Kurt Schneider Scientific Award (2010), the Hans-Jörg Weitbrecht-Preis für Klinische Neurowissenschaften (2011), the ECNP Neuropsychopharmacology Award (2012), the Prix ROGER DE SPOELBERCH (2014), and the 2016 CINP Lilly Neuroscience Clinical Research Award.

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Chris Oliver

Chris Oliver is Professor of Neurodevelopmental Disorders at the University of Birmingham and director of the Cerebra Centre for Neurodevelopmental Disorders. He trained as a clinical psychologist at Edinburgh University before completing a PhD on self-injurious behaviour in people with intellectual disability at the Institute of Psychiatry, London. He is currently researching early intervention, behaviour disorders in people with severe intellectual disability and autism spectrum disorder, behavioural, cognitive and emotional phenotypes in genetic syndromes and neuropsychological and behavioural assessment for people with severe intellectual disability. He has published over 180 peer reviewed articles in scientific journals, was previously Editor in Chief for the Journal of Intellectual Disability Research and serves on a number of scientific advisory committees for autism and syndrome support groups. Summaries of research are available at www.findresources.co.uk.

Jacqui Rodgers

Professor Jacqui Rodgers is an autism researcher based at the Institute of Neuroscience, Newcastle University, UK. Her work focuses on the interactions between core characteristics of autism and co-occurring mental health conditions. She has a particular interest in anxiety in autism and the interactions between anxiety and some of the core features of autism, including restricted and repetitive behaviours and sensory processing differences. With colleagues she developed the first anxiety questionnaires specifically designed and validated for autistic children and adults. She is also involved in the development and evaluation of a range of mental health focussed intervention programmes for autistic children and adults. This work is done in collaboration with members of the autism community at all stages of the research cycle. She works regularly with autistic children and their families and is patron of SPARCS, a registered charity, which aims to provide help and support to parents of children with autism and related conditions.

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Gaia Scerif

I am originally from Milan, Italy, but after an International Baccalaureate at the United World College of Southern Africa (Swaziland), I decided not to settle for a while. I completed a BSc in Psychology at the University of St. Andrews, Scotland, spending a year as a visiting student at Queen's University in Canada. I then read for a PhD in developmental cognitive neuroscience at the Institute of Child Health, University College London. After a brief visiting fellowship at the Sackler Institute of Developmental Psychobiology, Cornell University and Weill Medical School (New York), I held a permanent appointment as a lecturer at the School of Psychology, University of Nottingham. I have been based at the University of Oxford since 2006.

My research focuses on the processes underlying the development of attentional control and those underlying attentional difficulties, from their neural correlates to their outcomes on emerging cognitive abilities. Addressing these questions involves combining the study of typical attentional control with research on atypical neurocognitive development affecting molecular pathways and neural circuits involved in attentional control: (1) difficulties associate with a well-defined genetic aetiology (e.g., fragile X syndrome, Williams syndrome, Down syndrome, sex chromosomal trisomies); and (2) complex behavioural syndromes of mixed aetiology (e.g., AD/HD).

Cristiane Silvestre di Paula

Dr. Cristiane Silvestre de Paula is a Professor in the Program of Developmental Disorders at Universidade Presbiteriana Mackenzie and Senior Researcher at Department of Psychiatry at Universidade Federal de São Paulo, in São Paulo, Brazil. Her research expertise is in the area of child mental health, with a focus on epidemiological studies in Autism. Dr. Silvestre de Paula has a long experience in international studies and 85 peer reviewed articles in scientific journals with and H-index = 30, taken from Google Scholar. She is Handling Editor of the British Journal Psychiatry Open and member of the Editorial Board of the Brazilian Journal of Psychiatry. She also member of the International Autism Epidemiology Network - IAEN (since 2017) and of the Latin American Autism Spectrum Network – REAL (since 2015).

Andrew Stanfield

Dr Andrew Stanfield is the Director of Clinical Research at the University of Edinburgh's Patrick Wild Centre, a translational research centre with particular interests in monogenic causes of Intellectual disability and autism. His research has an overarching focus on the translation of fundamental neuroscience into the development and testing of new therapies for people with these conditions. He is also an Honorary Consultant in the Psychiatry of Learning Disabilities in Southeast Scotland, as well as a medical / scientific advisor to the UK Fragile X Society and to Bridge the Gap, an international support organisation for families affected by SYNGAP1 related intellectual disability.

Michael Thomas

Since 2010, Michael Thomas has been Director of the University of London Centre for Educational Neuroscience, a cross-institutional research centre which aims to advance translational research between neuroscience and education, and develop practical applications within education. In 2003, Michael established the Developmental Neurocognition Laboratory within Birkbeck's world-leading Centre for Brain and Cognitive Development. The focus of his laboratory is to use multi-disciplinary methods to understand the brain and cognitive bases of cognitive variability, including developmental disorders and individual differences. Within educational neuroscience, his work includes understanding the role of inhibitory control in children's science and math learning, investigating the influence of cell phone use on adolescent brain development, linking findings on sensitive periods in brain development to their educational implications, and building links between genetics, environment and education in children's developmental outcomes. His work on developmental disorders includes current projects on childhood development in Williams syndrome, Down syndrome, Fragile X, and autistic spectrum disorder. In 2006, his research lab was the co-recipient of the Queen's Anniversary Prize for Higher Education, for the project "Neuropsychological work with the very young: understanding brain function and cognitive development". Michael is a Chartered Psychologist, Fellow of the British Psychological Society, Fellow of the Association for Psychological Science, and Senior Fellow of the Higher Education Academy.

Annalu Waller

chartered rehabilitation engineer, she manages a number of interdisciplinary research projects developing intelligent and multimodal technologies within the field of Augmentative and Alternative Communication (AAC) and is director of the Dundee AAC Research Group (aac.computing.dundee.ac.uk). She has worked in the field of AAC since 1985. She is passionate about leveraging "intelligent computing" to develop communication support for individuals with severe language and communication needs. Her primary research areas are human centred computing, natural language processing, personal narrative and assistive technology. In particular, she focuses on empowering end users, specifically disabled adults and children, by involving them in the design and use of AAC technology. She co-directs two unique interdisciplinary MSc degree programmes: in AAC with Psychology; and in the Design of Healthcare and Assistive Technologies with Biomedical Engineering at Dundee. She has spearheaded the integration of AAC into undergraduate and postgraduate teaching in computing, education, medicine and dentistry. She is on the editorial boards of several academic journals and sits on the boards of a number of national and international organisations representing disabled people. She was awarded an OBE in the 2016 New Year's Honours List for services to people with Complex Communication Needs and is an Honorary Fellow of the Royal College of Speech and Language Therapists.

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Educational Day Programme

Educational Day

Venue – Aston University – Sumpner Theatre, Main Building (Room MB651)

Day One – Educational Day: Wednesday 4th September 2019	
08:45 – 09:45	**Registration and Coffee and pastries**
09:45 – 10:00	**Welcome from the Conference Organisers**
10:00 – 11:00	**Talk 1 – Keynote:** Dr. Andrew Stanfield – Precision medicine in the context of genetic neurodevelopmental disorders (Chair: *Honey Heussler*)
11:00 – 11:25	**Morning refreshments**
Exciting Methods Lightning Round: (Chair: *Kate Woodcock / Jane Waite*)	
11:25 – 12:40	**Free Communications** (15 min x 4 plus 15 min Q&A)
	Talk 2: *F. Ehrhart* – Creating Rare Disease Pathways Using Existing Data
	Talk 3: *C. Carey* – Proton Magnetic Resonance Spectroscopy for Identifying Pathways to Developmental Outcomes
	Talk 4: *P. de Vries* – Community Based Participatory Research in the Context of Behavioural Phenotypes
	Talk 5: *G. Porter* – Non-Invasive Pre-natal Screening, What Parents Think.
	Questions on Session – 15 mins
12:40 – 13:40	**Talk 6 – Keynote:** Prof. Andreas Meyer-Lindenberg – Behavioural Phenotypes and the Transdiagnostic Nature of Neurodevelopmental Disorders (Chair: *Anna Jansen*)
13:40 – 14:30	**Lunch**
14:30 – 15:30	**Talk 7 – Keynote:** Prof. Louise Gallagher – Building Neurodevelopmental CNV Carrier Cohorts for the Advancement of Knowledge on Genetic and Neurodevelopmental Disorders (Chair: *Anna Jansen*)
15:30 – 16:30	**Talk 8 – Keynote:** Prof. Richard Hastings – A Family Systems Perspective on Rare Genetic Syndromes (Chair: *Jane Waite*)
16:30 – 16:55	**Afternoon refreshments**
16:55 – 17:55	**Talk 9 – Keynote:** Prof. Annalu Waller – Collaborating with Stakeholders in the Design of Digital Assistive Technology Interventions (Chair: *Kate Woodcock*)
	Close of Day 1
18:00 – 18:30	**Guided Walk to Conference Reception**
18:30 – 20:00	**Conference Welcome Reception –** the Library of Birmingham

Research Symposium Programme

Research Symposium

Venue: Conference Aston

Day Two – Research Symposium: Thursday 5th September 2019	
08:00 – 08:50	**Registration and Poster Set-up** **Coffee & Pastries**
08:50 – 09:00	**Welcome**
SESSION 1: (Chair: *Kate Woodcock*)	
09:00 – 09:45	**Talk 10 – Keynote:** *Prof. Chris Oliver* – The Importance of Knowing When to be Precise: There's Both a Lumper and a Splitter in all of us
09:45 – 10:45	**Careful Phenotyping** (3 Free Communications: 15 min + 5 min Q&A)
	Talk 11: *E. Baker* – Incomplete Silencing of Full Mutation Alleles in Males with Fragile X Syndrome is Associated with Autistic Features
	Talk 12: *J. Harris* – Back to Basics in Lesch Nyhan Syndrome; the Paradigm for a Behavioural Phenotype
	Talk 13: *S. Mous* – Genotype and Cognitive and Behavioural Phenotypes in Children and Adolescents with Neurofibromatosis Type 1
10:45 - 11:15	**Morning refreshments and Poster Viewing**
SESSION 2: (Chair: *Caroline Richards*)	
11:15 – 12:00	**Talk 14 – Keynote:** *Prof. Michael Thomas* – Computational Modelling of Interventions for Developmental Disorders
12:00 – 12:40	**Sleep and Behaviour** (2 Free Communications: 15 min + 5 min Q&A)
	Talk 15: *G. Agar* – The Developmental Trajectory of Sleep in Children with Smith-Magenis Syndrome Compared to Typically Developing Peers
	Talk 16: *H. Heussler* – The Impact of Seizure and Gastroesophageal Reflux History on Sleep and Behaviour in Angelman Syndrome
12:40 – 13:45	**Lunch and Poster Session**
SESSION 3: (Chair: *Jane Waite*)	
13:45 – 14:30	**Talk 17 – Keynote:** *Prof. Gaia Scerif* – Understanding Variable Outcomes in Disorders of Identified Genetic Aetiology: The Importance of Early and Deep Developmental Phenotyping
14:30 – 15:30	**The development of behavioural and cognitive phenotypes** (3 Free Communications: 15 min + 5 min Q&A)
	Talk 18: *E. Pearson* – The Development of Gesture and Prelinguistic Communication in Angelman Syndrome
	Talk 19: *H. Crawford* – Changes in Behaviour Across the Lifespan in Fragile X Syndrome
	Talk 20: *G. Edwards* – Repetitive Behaviour in Rubinstein-Taybi Syndrome: A 12-Year Follow-Up

Day Two – Research Symposium: Thursday 5th September 2019	
15:30 - 16:00	**Afternoon refreshments and Poster Viewing**
SESSION 4: (Chair: *Raja Mukherjee*)	
16:00 – 16:35	**ASD & genetic syndromes** (3 Free Communications: 10 min. Questions at end of session)
	Talk 21: *A. Welham* – Concordance of the SCQ and ADOS in Identifying Autism Symptomatology in Genetic Syndrome Groups
	Talk 22: *J.M. Glennon* – Visual Perception as a Window into the Nature of Autistic-Like Trait Expressions in Down Syndrome and Fragile X Syndrome
	Talk 23: *K. Baker* – How Does Genetic Diagnosis Influence Autism in Children with Intellectual Disability?
	Questions on Session – 5 mins
SESSION 5: (Chair: *Hayley Crawford*)	
16:35 – 17:10	**Social Cognition** (3 Free Communications: 10 min. Questions at end of session)
	Talk 24: *M. Otter* – Social Cognition Deficits in Adults with Triple X Syndrome
	Talk 25: *J. Wolstencroft* – Genetics and Social Cognition: Developmental Changes in Emotion Recognition in Turner Syndrome
	Talk 26: *Ellis, K.* – Social Cognition, Social Interaction and Social Behaviour in Cornelia de Lange, Fragile X and Rubinstein-Taybi Syndromes
	Questions on Session – 5 mins
17:15 – 18:00	**Talk 27 – Keynote – The Tom Oppé Distinguished Lecture:** *Professor Louise Gallagher* – Genes, Family, Time and Place: Challenges in Studying Behavioural Phenotypes (Chair: *Honey Heussler*)
	Close of Day 1
19:30* – 23:00	**Gala Dinner –** Birmingham Botanical Gardens *Arrival from 19:00 for 19:30 start

Day Three – Research Symposium: Friday 6th September 2019	
08:30 - 09:00	**Registration** (for new arrivals) **and Coffee & pastries**
SESSION I: (Chair: *Andre Strydom*)	
09:00 – 09:45	**Talk 28 – Keynote – The Genetics Society Lecture:** *Dr. Cristiane Silvestre de Paula* – ASD Across Latin America: Diagnosis, Challenges, and Barriers to Care

Day Three – Research Symposium: Friday 6th September 2019	
09:45 – 10:45	**Health and Disease** (3 Free Communications – 15 min + 5 min Q&A)
	Talk 29: *R. Hithersay* – Longitudinal Changes in Cognition in the LonDownS Cohort
	Talk 30: *C.B. Eaton* – Prevalence and Aetiology of Epileptic Seizures in Young People with 22q11.2 Deletion Syndrome and Relationships with Other Neurodevelopmental Disorders
	Talk 31: *D. McDonald-McGinn* – Correlation of Congenital Heart Disease Severity with Developmental Outcome in Patients with 22q11.2 Deletion Syndrome
10:45 - 11:15	**Morning refreshments and Poster Viewing**
SESSION 2: (Chair: *Patricia Howlin / Petrus de Vries*)	
11:15 – 12:00	**Talk 32 – Keynote:** *Dr. Andrew Stanfield* – SYNGAP1 Related Intellectual Disability: Understanding the Phenotype to Move Towards Trials
12:00 – 13:00	**Treatment Approaches for Behavioural Phenotypes** (3 Free Comms' – 15 min + 5 min Q&A)
	Talk 33: *C. Samango-Sprouse* – The Relationship Between 47,XXY (Klinefelter syndrome), Autism Spectrum Traits (AST), and Early Hormonal Therapy (EHT)
	Talk 34 – The Pat Howlin Lecture: *Jeanne Wolstencroft* – SOAR Study: New Approaches to Managing Social Skills Deficits in Turner Syndrome
	Talk 35 – The Leclezio-de Vries Lecture: *Siobhàn Blackwell* – Collaborating with Stakeholders on the Development of a "Flexible Scheduling" Early Intervention Approach Designed to Prevent Disabling Resistance to Change
13:00 – 14:00	**Lunch and Poster Viewing**
14:00 – 14:45	**Talk 36 – Keynote:** Prof. Deborah Fidler – Executive Function and Goal Directed Behaviour in People with Down Syndrome (Chair: *Jane Waite*)
14:45 – 14:55	**Presentation from the SSBP Oslo 2020 Conference Team**
14:55 – 16:05	**SSBP AGM and Award Ceremony**
	Afternoon Refreshments
SESSION 3: (Chair: *James Harris*)	
16:05 – 16:30	**Mental Health** (2 Free Communications: 10 min. Questions at end of session)
	Talk 37: *L. Groves* – The Application of Attentional Control Theory for Anxiety in Cornelia de Lange Syndrome
	Talk 38: *Gray, K.* – Mental Health Outcomes in Adults with Autism
	Questions on Session – 5 mins
16:30 – 17:15	**Talk 39 – Keynote:** *Dr. Jacqui Rodgers* – Restricted & Repetitive Behaviours: Impact, Associations and Uncertainties
17:15 – 17:30	**Close of Research Symposium**

Abstracts for Educational Day

(in order of presentation)

1 – KEYNOTE: Precision Medicine in the Context of Genetic Neurodevelopmental Disorders

Andrew Stanfield
University of Edinburgh

For many years the vast majority of intellectual disability was felt to be idiopathic in nature. However, with increasingly sophisticated genetic investigation becoming routinely available, it has become apparent that many cases arise from variants in key genes involved in brain development. By modeling these variants in the laboratory, it becomes possible to understand how they perturb brain function and identify potential targets for intervention. This raises the possibility of developing targeted treatments for genetic developmental disorders.

2: Linking Genotype to Phenotype by Biological Pathways

***Ehrhart F.*[1,2], *Slenter D.N.*[1], *Bahram Sangani N.*[1,2], *Willighagen E.L.*[1], *Curfs L.M.G.*[2], *Evelo C.T.*[1]**

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[2] *GKC-Rett Expertise Centre, Maastricht University Medical Centre, Maastricht, The Netherlands*

Background: Mutations causing rare diseases in humans are valuable to study, as they not only allow us to investigate rare metabolic or gene signalling aberrations, but also tell us about normal functioning. Investigation of downstream pathways inevitably leads from a mutated gene to a more or less characteristic phenotype. Structuring this existing knowledge, based on text and data mining and expert curation, allows these pathways to serve as prior knowledge networks to be used in data analysis. The European Joint Programme on Rare Diseases (EJP-RD, started 1.1.2019) has recognised this task and made it a part of the cross-omics data analysis work-package.

Methods: Creation of rare disease pathways was done using recent literature (including text mining), data mining from databases containing protein-protein interactions and known regulatory actions, and expert input. The pathways were drawn using PathVisio software, annotated with Ensembl or UniProt identifiers (for genes and gene products) or ChEBI identifiers for metabolites. Interactions were annotated with Molecular Interaction Maps (MIM). The pathways were uploaded to the open pathway database WikiPathways, to allow for regular expert curation and updates.

Results: Currently (2019-04-11) there are 23 pathways available in the rare disease portal of WikiPathways (of in total 2752 pathways (all species, human pathways: 1067). Fifteen (and increasing) of these pathways are from a medical guidelines book on rare metabolic diseases (by N. Blau). Proof of principle studies with e.g. Rett syndrome showed that combination of these prior knowledge pathways and gene expression data allows fast and precise insights into disease mechanisms.

Conclusion: Structuring molecular knowledge about rare diseases in a machine and human readable manner allows using this knowledge for advanced data analysis. Further work will focus on creation of pathways needed by the rare disease community, e.g. the European Reference Networks (ERNs) or the SSBP.

Keywords: pathway analysis, WikiPathways, omics data analysis, linked data, pathway database

3: Subcortical Biochemistry in Newborns with and without a Family History of Neurodevelopmental Conditions and Their Developmental Outcomes at 14 – 16 Months

Carey C.[1,2,3], Potes I.[1,2], Ciarrusta J.[1,2], Dimitrova R.[1,2], Kangas J.[1], Javed A.[1], Perry E.[1], Allsop J.M.[2], Fox M.[2], Hughes E.[2], Rutherford M.[2], Murphy D.[2,3], McAlonan G.[2,3]

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[2] *Centre for the Developing Brain, Division of Imaging Sciences and Biomedical Engineering, King's College London, UK*

[3] *NIHR Biomedical Research Centre for Mental Health at the South London and Maudsley NHS Foundation Trust and King's College London, UK.*

Background: Neurodevelopmental conditions such as Autism spectrum disorder (ASD) and ADHD are typically diagnosed at 3-4 years of age or later, but pathology starts much earlier.

Methods: We examined the relationship between proton-Magnetic Resonance Spectroscopy measured subcortical Glutamine-Glutamate (Glx; a proxy of the glutamate neurotransmitter pool) and N acetyl aspartate (NAA; a neuronal marker) in infants at 6 months (low oral dose of chloral hydrate was used to promote sleep) and cognitive outcomes at 14-16 months (Mullen Scales of Early Learning). To capture a developmental spectrum, the cohort (n = 45) also included infants 'at-risk' of neurodevelopmental difficulties (n = 19) with a first degree relative with ASD or ADHD. The relationships between metabolites at 6 months and Mullens scores at 14 months were examined using parametric (Pearson) or non-parametric (Spearman) correlations as appropriate.

Results: There was no difference in Glx or NAA at 6 months in infants with and without a family history of neurodevelopmental conditions, therefore the relationship between metabolites and cognitive measures was examined across the whole group. There was a positive correlation between the Mullens cognitive T score at 14-16 months and both infant Glx ($r(36)=0.38$, $p=0.02$) and NAA ($r(39)=0.32$, $p=0.046$). On post hoc analysis of the Mullens sub-scores, this was largely explained by a positive correlation between the Visual Reception Scale and both infant Glx ($r(41)=0.36$, $p=0.02$) and NAA ($r(41)=0.32$, $p=0.02$).

Conclusion: The Visual Reception Scale of the Mullens is considered a measure of non-verbal intelligence in childhood. Our findings suggest that markers of the glutamate excitatory system and neuronal 'health' at 6 months predict cognitive outcome. This may have implications for identifying and targeting help to infants in more need of support. However, these findings should be considered preliminary and await replication; further assessment at later time points is planned.

Keywords: Autism, neurodevelopmental, MRS, Glx, NAA, Mullens

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4: Community-Based Participatory Research in the Context of Behavioural Phenotypes

de Vries P. J.*[1], *Jansen A.*[2] *& the TANDem project team

[1.] *Division of Child & Adolescent Psychiatry, University of Cape Town, South Africa*

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Community-based participatory research (CBPR) is defined as a collaborative approach to research that involves all partners in highly equitable ways in all phases of the research process. It recognizes the unique strengths brought by all stakeholders, some of whom will contribute 'technical' expertise, and others 'lived' or 'contextual' expertise. CBPR was conceptualized not so much as a research 'methodology' but more as a research philosophy. Starting with a topic of importance to the community, the goal is to combine knowledge and action towards social change that will ultimately improve community health and eliminate health disparities.

In this presentation, we will use Tuberous Sclerosis Complex (TSC) as an example of community-based participatory research. TSC is a rare genetic disorder associated with a vast range of physical and neuropsychiatric manifestations. Over the last few decades identification and treatment of the physical features of the disorder has improved significantly, but the assessment and treatment gap for the TSC-associated neuropsychiatric disorders (TAND) has remained. Here we will describe how we joined with Tuberous Sclerosis International (TSCi), the umbrella organization for all national TSC non-profit organisations, in two related projects in an effort to meet the goals of CBPR.

Keywords: Community-based participatory research; participatory research; behavioural phenotypes, tuberous sclerosis, socially-responsive research

5: Non-Invasive Prenatal Screening (NIPT): Opinions from a Survey to Parents of Children with X and Y Chromosomal Variations (XYV)

***Porter G.*[1], *Lasutschinkow P.*[1], *Tran S.*[1], *Samango-Sprouse C.*[2,3,1], *Sadeghin T.*[1], *Gropman A.*[4]**

[1] *The Focus Foundation, USA*

[2] *Department of Pediatrics, George Washington University, USA*

[3] *Department of Human and Molecular Genetics, Florida International University, USA*

[4] *Department of Neurodevelopmental Disorders and Neurogenetics, Children's National Medical Center, USA*

Background: The introduction of NIPT has allowed low-risk and younger families to prenatally identify foetuses at-risk for XYVs. This study aims to investigate the attitudes towards NIPT in parents of a child with a diagnosis of an XYV.

Methods: Parents of young children with XYVs completed a survey regarding their opinions of NIPT.

Results: 55 participants responded to the survey, the majority of whom had a child diagnosed with 47,XXY (58.2%). Of the twenty-three prenatally diagnosed participants who used NIPT, 95.7% believed NIPT had a positive impact on their life, stating: "I had several months of being pregnant to understand and prepare for my [child]." The positive impact of NIPT was reported because parents were able to research and learn about the disorders (35.3%), arrange resources and possible interventions (38.2%), and identify possible indicators of neurodevelopmental delays prior to delivery (20.6%). 85.5% of all participants would recommend NIPT as a resource given the new information they received from the survey. 89.1% of all participants expressed that they would utilize NIPT as a resource for future pregnancies.

Conclusion: This study documented parental opinions of the importance of NIPT for identifying those at-risk for XYVs. The majority of prenatally diagnosed participants indicated that NIPT had a positive impact on their life because they were able to prepare emotionally and gather resources to care for a child with an XYV. However, parents also reported a need for counselling and education to medical providers regarding NIPT, potential diagnoses, and various methods to share stressful information. This survey indicates positive parental opinions of NIPT and its future use, as well as the family's desire for information on NIPT and potential postnatal resources. Further research examining parental perspectives will assist medical providers in giving personalized care to expectant families in order to improve outcomes and well-being.

Keywords: Non-invasive prenatal testing, NIPT, Prenatal diagnosis, Sex chromosome aneuploidies (SCAs), Klinefelter's syndrome, 47,XXY

6 – KEYNOTE: Behavioural Phenotypes and the Transdiagnostic Nature of Neurodevelopmental Disorders

Andreas Meyer-Lindenberg
Central Institute of Mental Health, Heidelberg University/Medical Faculty Mannheim

Current nosological categories in psychiatry lack a biological definition and are thus necessarily heterogeneous from a mechanistic point of view. In order to progress to individualized therapies, this motivates a research strategy that investigates the neural substrate of disorder-associated behaviours that are often transdiagnostic. Functional brain imaging has provided insights into the nature of brain dysconnectivity in mental illness. We propose that genetic and environmental risk factors converge upon systems-level circuits for several core dimensions of cognition, producing transdiagnostic symptoms. We argue that risk-associated disruption of these circuits mediates susceptibility to broad domains of psychopathology rather than discrete disorders. By combining neuroimaging with ecological momentary assessment, we find that specific risk/resilience circuits are linked to everyday behaviours, such as social interactions or movement, and context factors, such as urban or natural environments, that help explain interindividual variation in risk that can be utilized for precision therapy and precision prevention strategies.

Keywords: Transdiagnostic phenotypes, research domain criteria, dysconnectivity, environmental risk, resilience, precision prevention

7 – KEYNOTE: Building Neurodevelopmental CNV Carrier Cohorts for the Advancement of Knowledge on Genetic and Neurodevelopmental Disorders

Louise Gallagher
School of Medicine, Trinity College Dublin (on behalf of the MINNDS Network).

Neurodevelopmental structural copy number rearrangements or variants (ND-CNV) are known to confer risk for a range of neuropsychiatric conditions, including intellectual disability, autism and schizophrenia. These are rare but recurrent rearrangements that may be inherited or arise de novo. They are more highly penetrant for early onset neurodevelopmental conditions, such as autism and intellectual disability, however also associated with of moderate penetrance for schizophrenia, with reported odds ratios (OR) in the order of 2-30. ND-CNV also show pleiotropic effects, i.e. the same variant may be associated with different outcomes that may range from subtle cognitive deficits in non-clinical samples to severe and highly impairing neurodevelopmental disorders.
Research in ND-CNV is assisting with our understanding of neurobiology and may support drug development for neurodevelopmental conditions. However there is significant variability in clinical outcomes that merits further investigation to better understand the associated clinical phenotypes and to provide more certainty in genetic counselling, particularly for later onset neuropsychiatric conditions. It is likely that additional risk factors mediate the effects of ND-CNV and if identified may also help inform prevention strategies.
The relative rarity of ND-CNV is a major challenge to meaningful research. Transnational approaches are required to build cohorts of ND-CNV carriers who may participate in research. The Maximising Impact of Research in Neurodevelopmental Disorders (MINDDS) COST network is a European network that aims to build capacity to study NDD-CNVs. The objective of the network is to develop a collaborative network to identify individuals who possess pathogenic CNV, agree standardized assessments and research protocols and facilitate data sharing and knowledge exchange for the benefit of researchers, clinicians and patients and to inform our understanding of the ethical, legal and social considerations of NDD-CNV research. In addition it provides opportunities for training and knowledge exchange for young researchers.
In the talk I will give an update of our understanding of rare ND-CNV and their role in neurodevelopmental disorders and traits, future research directions and efforts to develop ND-CNV cohorts through the MINDDS network.

Keywords: Neurodevelopmental disorders, genomics, copy number variants, cohorts, phenotyping

8 – KEYNOTE: A Family Systems Perspective on Rare Genetic Syndromes

Richard P. Hastings
Centre for Educational Development Appraisal and Research, University of Warwick, UK
Centre for Developmental Psychiatry and Psychology, Monash University, Australia

One of the major influences on all children's development is their experience of family life. Most research about the families of children with rare genetic syndromes focuses on familial genetic dimensions, or on the impact of having a child with a genetic syndrome on parents' psychological well-being. This focus fails to recognise that families are systems: all members of a family, and all family sub-systems (e.g., parent-child, couple, sibling-sibling) influence each other. The main implications of a systems perspective are: 1. That it is important to consider the well-being of family members other than parents (e.g., siblings and extended family members), 2. That the development of a child with a rare genetic syndrome may be affected by the functioning of other family members and by the day-to-day routines and activities of the family, and 3. That there may be broader contextual influences on the family (such as poverty, and culture) that will influence the child with a rare syndrome and their family members. Family systems approaches also do not simply consider negative outcomes for family members. Thus, it is also important in research to explore potential positive outcomes and experiences of family members. In this presentation, I will explore these dimensions of family systems thinking and illustrate each key point with research findings about children with developmental disabilities and their families; drawing on research about the families of children with rare genetic syndromes wherever possible. Implications for practitioners and for family support will also be considered.

Keywords: Family systems; parents; siblings; psychological distress; positive perceptions

9 – KEYNOTE: Collaborating with Stakeholders in the Design of Digital Assistive Technology Interventions

Annalu Waller
School of Science and Engineering, University of Dundee, Dundee, UK

Digital Assistive Technologies (dATs) have the potential to transform the lives of persons with complex communication needs, especially in the form of Augmentative and Alternative Communication (AAC) technologies. Unlocking this potential requires an inter-disciplinary user-centred approach which actively engages a diverse range of stakeholders in all stages of software innovation from ideation through to product evaluation. Traditional user-centred design focusses on understanding the context in which the technology will be deployed and working with designers to identify system requirements and to co-design prototype solutions. Final products are evaluated with end users to ensure evidence-based technology adoption. End users share their experience and insights by participating in activities such as focus groups, interviews, design workshops and summative evaluations, all of which rely on communication and physical manipulation. Meaningful involvement of stakeholders in the design of dAT therefore raises practical and ethical challenges, especially when designing interventions for children, young people and adults with severe physical and/or intellectual disabilities. Research into the design of dAT at Dundee University has demonstrated that disabled individuals can be empowered as expert users alongside their families, carers, educators and rehabilitation professionals. This involves employing methodologies such as ethnographic research to gain a greater understanding of the problems to be solved and the complex environments in which technology is to be deployed. This keynote will explore how people with complex communication needs, and those who interact with them, have been empowered to have a voice in the design of dAT by adapting design methods and training end users to engage in co-design. The practical and ethical challenges will be addressed with a view to developing systems which meet the needs of the diversity of end users. The Developmental Trajectory of Sleep in Children with Smith-Magenis Syndrome Compared to Typically Developing Peers

Keywords: Augmentative and Alternative Communication (AAC); Digital Assistive Technology; Co-Design; User-Centred Design

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Abstracts for Research Symposium Day 1 *(in order of presentation)*

10 – KEYNOTE: The Importance of Knowing When to be Precise: There's Both a Lumper and a Splitter in all of us.

Chris Oliver
Cerebra Centre for Neurodevelopmental Disorders, School of Psychology, University of Birmingham, Birmingham, UK

As the rapid expansion of published research in behavioural phenotypes continues, the dimensions of difference across and within syndrome groups are becoming better defined. More precise description of behaviour has revealed nuanced but important differences in classes of behaviour previously combined under terms such as challenging and self-injurious behaviour. This is an important shift as causal models have subsequently become more refined to cater for different behavioural outcomes and this has elucidated differences in underlying causal pathways for specific behavioural outcomes. Research addressing these pathways has shown that executive function, physical difference and disorder, emotion, sensory experience, social cognition and social motivation are each demonstrably related to specific behavioural outcomes. As these dimensions and the resultant behavioural outcomes become better delineated and profiled, the importance of using more precise terms and concepts has become increasingly apparent and should be more widely adopted in clinical practice and related policy.

Alongside the refinement of behavioural phenotypes and causal pathways, the precise genetic causes of syndromes are also increasingly differentiated. In Cornelia de Lange, Angelman, Smith-Magenis and Prader-Willi syndromes for example, there is more than one underlying genetic difference and within syndrome behavioural outcomes that result from difference in genetic cause are well documented. These differences point to the need for identification of genetic subgroups in classic behavioural phenotype designs.

In combination these trends in genotype and phenotype research have implications for research designs (participant numbers must be greater if within syndrome genotypic difference is an organising variable), research methods (differentiating cognitive domains may require more testing to identify specific pathways), clinical practice (the targets for psychological intervention become increasingly personalised and less manualised) and policy (are guidelines at the level of all behavioural outcomes for all people with any syndrome likely to be effective or are guidelines for rare variants of genetic cause within one syndrome for a specific behavioural outcome likely to be adopted). These tensions may mean that even the most ardent splitter may have to let their inner lumper have a say.

Keywords: Behavioural phenotype, splitter, lumper

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11: Incomplete Silencing of Full Mutation Alleles in Males with Fragile X Syndrome is Associated with Autistic Features

Baker E.K.[1,2,3]*, Arpone M.*[1,2,4]*, Aliaga S.M.*[1]*, Bretherton L.*[4]*, Field M.*[5]*, Rogers C.*[5]*, Santa Maria L.*[6]*, Alliende A.M.*[6]*, Amor D.J.*[7,2]*, Godler D.E.*[1,2]

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[2] *Department of Paediatrics, University of Melbourne, Australia*

[3] *School of Psychology and Public Health, La Trobe University, Australia*

[4] *Brain and Mind, Murdoch Children's Research Institute*

[5] *Genetics of Learning Disability Service, Hunter Genetics, Australia*

[6] *Molecular and Cytogenetics Laboratory, INTA, University of Chile, Chile*

[7] *Neurodisability and Rehabilitation, Murdoch Children's Research Institute, Australia*

Background: Fragile X syndrome (FXS) is a common monogenic cause of intellectual disability (ID) and autism spectrum disorder (ASD). While it is caused by loss of the *FMR1* product (FMRP), mosaicism for active and inactive ***FMR1*** alleles, including pre-mutation (PM: 55-199 CGGs) alleles, is not uncommon. Both PM and active full mutation (FM: >= 200 CGGs) alleles often express elevated mRNA levels that are thought to be toxic. This study determined if complete *FMR1* mRNA silencing from FM alleles and/or levels of *FMR1* mRNA (if present) in blood are associated with intellectual functioning and autism features in FXS.

Methods: This study comprised a large international cohort of 98 individuals (70.4% male) with FXS (FM-only and PM/FM mosaic) aged 1-43 years. Participants completed an age appropriate developmental or intellectual functioning assessment and the Autism Diagnostic Observation Schedule-2nd Edition. *FMR1* mRNA was analysed in venous blood collected at the time of assessment, using the real-time PCR relative standard curve method.

Results: FM-only males (aged < 19 years) expressing FM *FMR1* mRNA had significantly higher ADOS calibrated severity scores compared to FM-only males with completely silenced *FMR1* ($p = 0.011$). Though, there was no significant differences between these sub-groups on intellectual functioning scores. In contrast, decreased levels of *FMR1* mRNA were associated with decreased intellectual functioning in FXS males ($p = 0.029$), but not autism features, when combined with the PM/FM mosaic group.

Conclusions: Incomplete silencing of toxic FM RNA may be associated with autistic features, but not intellectual functioning in FXS males aged under 19 years. While decreased levels of mRNA, may be more predictive of intellectual functioning, than autism features. These findings may have implications for patient stratification, design of pre-clinical and clinical trials, and outcome measure development in FXS; though replication in larger independent samples is required.

Keywords: Fragile X syndrome, FMR1 mRNA, Autism, intellectual disability, mosaicism

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12: Back to Basics in Lesch Nyhan Syndrome; the Paradigm for a Behavioural Phenotype

Harris J.
The Johns Hopkins University School of Medicine

Background: In 1973 William Nyhan introduced the term behavioural phenotype when describing self-injurious behaviour, typically self-biting in Lesch-Nyhan syndrome (LNS). The biting pattern involves the fingers, mouth and buccal mucosa and is asymmetrical. This rare, X-linked recessive neurogenetic syndrome is caused by deficiency of hypoxanthine-guanine phosphoribosyltransferase (HGprt), an essential enzyme in the purine salvage pathway. However, on further examination self-injury is not the only distinguishing feature, There is an extended behavioural phenotype best identified by investigating the spectrum of HPRT deficiency in classic LNS (less than 1%) and its variants LNV (2% to 20% enzyme). To clarify the phenotype behavioural and affective features of LND cases and variants (LNV) were quantified**.**
Methods: Study participants are a previously reported sample of 22 male patients with LND, 11 male patients with LNV, and 11 health male controls (NC) and one 20-year-old female with LND and her unaffected identical twin sister as control. Age range for subjects (12 to 38 years) and controls (11-39 years). HPRT enzyme activity levels were measured. Rating scales used were the CBCL, ABS-RC2 and individual ratings of topographies of self-injury. Neurocognitive profiles were completed in a subset of subjects.
Results: Classic LND cases had severe self- injury, interpersonal aggressive behaviour, anxious/depressive symptoms, inattention, and motor stereotypies in contrast to control subjects. LNV subjects were intermediate in these same features and did not self-injure. A neurocognitive profile was consistent across LND and LNV cases
Conclusions: A characteristic neurocognitive profile is consistent in LND and LNV cases. The extent of self-injury, behavioural and cognitive features are correlated with extent of HGprt enzyme deficit. These studies suggest the advantages in measuring dose response effects of the HGprt enzyme in both classical LNS and its variants to demonstrate the extended phenotype.

Keywords: Lesch Nyhan Syndrome, self-injurious behaviour, CBCL, ABS-RC2, behavioural phenotype, neuropsychological testing

13: Genotype and Cognitive and Behavioural Phenotypes in Children and Adolescents with Neurofibromatosis Type 1

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Background: Neurofibromatosis type 1 (NF1) presents a variable clinical phenotype and genetic factors have been suggested as important determinants of this variation. In this study, we describe the association between the NF1 genotype and cognitive and behavioural characteristics of a cohort of children with NF1 and of monozygotic twin pairs with NF1.

Methods: The records of all paediatric NF1 patients born between 1990-2013 seen at our NF1 outpatient clinic were reviewed. Intelligence (IQ) and parent-rated behavioural problems (global behavioural problems, ASD traits and ADHD symptoms) were assessed. Pathogenic NF1 variants were classified as likely to result in the absence of neurofibromin (group X) or as likely to result in the expression of abnormal neurofibromin (group P). Intra-class correlations (ICC) of IQ within monozygotic twin pairs were calculated and the effect of mutation type on IQ and behavioural problems was explored.

Results: The variability in IQ (87.6±15.4) in a cohort of children with NF1 (n=359) resembles the variability in the general population. Monozygotic twin pairs with NF1 (n=11) show the same high ICC as unaffected monozygotic twins (ICC=0.90). Individuals with group X mutations did not differ from individuals with group P mutations in IQ or global behavioural/emotional problems. However, the P group did show more ADHD symptoms (p=0.05) and more severe ASD traits (p=0.04).

Conclusion: The variability of cognitive function in our cohort of individuals with NF1 was not significantly different from the reference population indicating that the contribution of bi-allelic inactivation or specific genetic modifiers to IQ in NF1 is probably minimal. Notably, carriers of a group P mutation showed more severe ADHD and ASD symptoms (both on parent-report questionnaire and observational measure) compared to those with a group X mutation. Our study adds to the limited knowledge regarding the causes of variability in the cognitive and behavioural NF1 phenotype.

Keywords: Neurofibromatosis type 1, genotype-phenotype, cognition, behaviour

14 – KEYNOTE: Computational Modelling of Interventions for Developmental Disorders

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With respect to interventions, there can be an understandable disconnect between the work of clinicians and basic science researchers. The clinician is focused on improving behavioural outcomes, whereas the researcher is focused on understanding the underlying causes of deficits. The pathway between the two is not straightforward. One bridge between these approaches is the use of computational models, which can provide a foundation both to test causal models of developmental deficits and to explore the effectiveness of possible interventions. Based on a range of computational simulation results, I assess factors that influence the effectiveness of interventions for reading, language, and other cognitive developmental disorders. The analysis provides a level of mechanistic detail that is generally lacking in behavioural approaches to intervention. There were four main findings: (1) The exact nature of the neurocomputational deficit matters for the success of intervention, as well as its location in more complex cognitive architectures. (2) The timing of the intervention matters. (3) The content of the intervention with respect to the target behaviour matters. (4) Computational methods have not as yet revealed ways to trigger engagement of new compensatory mechanisms. Two areas remain little explored from this formal perspective: the implications of dosage, duration, intensity and regimes of behavioural interventions; and how to ensure generalisation beyond training items and persistence of intervention effects. I argue that together with advances in understanding the neural basis of developmental disorders and neural responses to training, formal computational approaches can spur theoretical progress to narrow the gap between the theory and practice of intervention.

Keywords: intervention, developmental disorders, computational modelling, connectionism.

15: The Developmental Trajectory of Sleep in Children with Smith-Magenis Syndrome Compared to Typically Developing Peers

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Background: Sleep is a developmental process crucial for many aspects of wake, yet little is known about its trajectory in individuals with neurodevelopmental disorders (NDDs). Research suggests individuals with certain NDDs are at greater risk of poor sleep than their typically developing (TD) counterparts. For example, individuals with Smith-Magenis syndrome (SMS) experience early-waking, night-waking and reduced total sleep time. However, despite elevated risk, little is known about how sleep develops over time in SMS. The current study compares sleep parameters of children with SMS over three years to explore whether sleep development is delayed or divergent in this group.

Methods: 20 children with SMS (*Mean* age = 8.89, *SD* = 2.65) and 50 chronologically age-matched TD children (*Mean* age = 7.76, *SD* = 3.28) completed objective actigraphy and informant-based assessments of sleep at Time 1. Thus far, 9 participants with SMS (*Mean* age = 10.70, *SD* =1.49) and 19 TD participants (*Mean* age = 10.55, *SD* =2.76) have completed identical assessments three years later at Time 2.

Results: Preliminary analysis indicates children with SMS have reduced total sleep time and prolonged waking after sleep onset compared to TD peers at both timepoints. Children with SMS also wake significantly earlier than TD children. Over time, sleep parameters diverge between groups. At Time 2, children with SMS have earlier bed times (p=.001) and poorer sleep efficiency (p=.003) compared to TD peers. Total sleep time reduced in the TD group (p=.004) but there was no significant change over time in the SMS group (p=.953).

Conclusion: The TD reduction in total sleep time reflects typical development of sleep, while the stability of sleep parameters in SMS suggests a divergent sleep trajectory. Overall, children with SMS experienced significantly poorer sleep. The implications of these findings for sleep interventions in people with SMS will be discussed.

Keywords: Sleep, trajectory, Smith-Magenis syndrome, development

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16: The Impact of Seizure and Gastroesophageal Reflux History on Sleep and Behaviour in Angelman Syndrome

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Background: Angelman Syndrome (AS) is a rare neurodevelopmental disorder affecting 1 in 15,000 to 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 longitudinal studies to advance research and therapeutics. This study describes preliminary clinical and behavioural outcomes.

Methods: Caregivers completed the Sleep Disturbance Scale for Children (SDSC; N=161) and a 29-item behavioural scale developed for Angelman Syndrome (N=184). Relationships between seizure and gastroesophageal history, and behaviour and sleep were explored.

Results: A history of seizures was associated with higher levels of excessive somnolence (*Mann-Whitney U* = 2,733.000, $p = .028$, $d = .336$), and greater incidences of spontaneous laughter/ smiling (*Mann-Whitney U* = 3,709.000, $p = .009$, $d = .406$), behaviour dysregulation (*Mann Whitney U* = 3,550.000, $p = .039$, $d = .318$), and repetitive behaviours (*Mann-Whitney U* = 3,566.000, $p = .042$, $d = .305$). A history of gastroesophageal reflux in infancy was associated with spontaneous laughter/ smiling (*Mann-Whitney U* = 2,973.500, $p = .016$, $d = .377$). Individuals with severe gastroesophageal reflux had higher levels of disordered breathing in sleep compared to individuals with mild cases (*Kruskal-Wallis* = 9.924, $p = .007$, $d = .796$). Medical treatment of gastroesophageal reflux was associated with higher levels of self-injury (*Mann-Whitney U* = 913.000, $p = .044$, $d = .388$) and repetitive behaviours (*Mann-Whitney U* = 1003.000, $p = .031$, $d = .454$). Spontaneous laughter/ smiling, anxiety and repetitive behaviours were associated with sleep disorders (*Spearman's r range* = .055-.361).

Conclusion: Repetitive behaviours, spontaneous laughter and self-injury may represent seizure activity or efforts to communicate discomfort associated with gastroesophageal reflux. Excessive somnolence may be a side effect of seizure activity or anti-epileptics, while disordered breathing may occur in sleep due to reflux.

Keywords: Angelman Syndrome, Patient-Driven Registry, Behaviour, Epilepsy, Sleep, Gastroesophageal Reflux

17 – KEYNOTE: Understanding Variable Outcomes in Disorders of Identified Genetic Aetiology: The Importance of Early and Deep Developmental Phenotyping

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With the increased availability of genetic testing, multiple genetic alterations have been associated with atypical developmental outcomes. These outcomes were at least initially classified as "generalised developmental delay". However, as a growing number of individuals receive diagnoses, there is both the clinical imperative and the research opportunity to find ways to implement deeper phenotyping, to reveal both general and more specific trajectories to cognitive outcomes for these individuals.

Today I will focus on evidence suggesting that an understanding of early individual differences in cognition, for these groups, may provide some clues to understanding their variable developmental trajectories. First, I will discuss longitudinal data from young children with fragile X syndrome, a group associated with high risk of attention deficits in childhood. A series of longitudinal findings, using methods that allow for deep phenotyping, suggests that early group-level and individual differences in attentional processes predict differences in later behavioural difficulties. The second line of research focuses on children with Williams syndrome and Down's syndrome, to suggest that differences in attention between and within these supposedly homogeneous syndrome groups, as well as individual differences in domain-specific skills, predict variable classroom outcomes in emerging literacy or numeracy. I will point to collaborative efforts with many colleagues who have long embraced the need to carry out deep and longitudinal phenotyping of multiple cognitive domains, but aim to do so more collaboratively.

A number of general conclusions emerge. First, links between genes, brain and cognition need to be situated in a developmental context, even in these relatively simple genetic disorders. Second, the increase in early diagnoses offers the opportunity to study developmental trajectories of risk and resilience for complex behaviourally-defined disorders that are in the main diagnosed much later in childhood, and their comorbidity. Finally, these findings suggest that the developmental outcome of these genetic differences is malleable, and understanding good outcomes, as well as weaknesses, may help guide more syndrome-specific and effective intervention.

Keywords: Early genetic diagnosis, early cognitive phenotype, developmental trajectories, variable risk

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18: The Development of Gesture and Prelinguistic Communication in Angelman Syndrome

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Background: Angelman syndrome (AS) is caused by deletion or inactivation of UBE3A. Minimal or absent speech is a core characteristic and there is a suggested dissociation between speech and non-verbal communication abilities, proposing an isolated speech production impairment in AS. Given that for both typical and clinical populations the emergence of prelinguistic communication, including gestures, can provide insight into concurrent and future language abilities, exploration of the development of prelinguistic communication in AS can ascertain to what extent developmental mechanisms underlie the absence of speech or whether it is related to the inactivation of UBE3A.

Methods: Questionnaire data were collected on comprehension, speech production and gesture use for children with AS (N = 40, M_{age} = 9.58, SD = 3.98). Gesture use, criteria of intentionality, communicative complexity, verbal and non-verbal communication were also assessed using behavioural coding (N = 47), M_{age} = 9.26, SD = 3.54).

Results: A strong, positive correlation was found between the number of communicative gestures and comprehension scores in AS (r_s = .725, p<.001), which was comparable to typically-developing children of similar comprehension abilities (r_s = .721, p<.001). Guttman scaling analysis showed that gestures and prelinguistic communication emerged in a reliable, ordered sequence (C_R = .959), that converged with the sequence seen in typical development, except for the presence of verbalisations.

Conclusion: Developmental mechanisms appear to underlie gesture use and prelinguistic communication in AS, suggestive of delay rather than impairment. In contrast, these mechanisms cannot account for the absence of speech, providing further evidence that this is an isolated impairment that could be related to the inactivation of UBE3A. These results have further implications for the use of standardised developmental assessments for individuals with AS, due to the reliance on spoken language, which may not accurately capture the developmental ability and communicative variability seen in AS.

Keywords: Angelman syndrome, communication, gesture, prelinguistic, development, intellectual disability,

19: Changes in Behaviour Across the Lifespan in Fragile X Syndrome

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Background: The behavioural phenotype of fragile X syndrome (FXS) encompasses a) behaviours associated with attention-deficit-hyperactivity-disorder (ADHD) including overactivity and impulsivity, b) behaviours associated with autism spectrum disorder (ASD) including social impairment and repetitive behaviour, and c) aggressive and self-injurious behaviours. However, little is known about how these behavioural characteristics change over time and how they interact with one another. We address this gap in knowledge across two longitudinal studies investigating change in behavioural characteristics over an eight year period in males with FXS. First, we investigate the profiles and developmental trajectories of overactivity, impulsivity, and repetitive behaviour, and whether these differ as a function of heightened ASD symptomatology. Second, we explore the persistence of aggressive and self-injurious behaviours and whether behavioural characteristics of ASD and ADHD are associated with, and can predict, persistence of aggressive and self-injurious behaviour.
Methods: Data on standardised informant measures of behavioural characteristics were collected at three time points spanning eight years from 69 (M_{age} = 17.38 years at Time 1) and 79 (M_{age} = 17.64 years at Time 1) males with FXS (Study 1 and Study 2, respectively).
Results: In Study 1, participants without elevated symptoms of autism at Time 1 showed a reduction in impulsivity and repetitive questioning over time, whereas those with elevated symptoms of autism did not. Results of Study 2 showed 77% and 69% persistence rates over eight years for self-injurious and aggressive behaviour, respectively. Baseline levels of repetitive behaviour predicted persistent self-injurious behaviour. Chronological age and baseline measures of impulsivity and overactivity were associated with persistent aggressive behaviour but only impulsivity *predicted* persistence of this behaviour.
Discussion: These studies offer novel insights into the behavioural phenotype of fragile X syndrome and associated risk factors. Identifying early risk markers of impairing behavioural features paves the way for targeted early intervention.

Keywords: fragile X syndrome, autism spectrum disorder, attention deficit hyperactivity disorder, self-injurious behaviour, aggressive behaviour, developmental trajectory

20: Repetitive Behaviour in Rubinstein-Taybi Syndrome: A 10-Year Follow-Up

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Background: Rubinstein-Taybi Syndrome (RTS) is caused by an alteration to the CREBBP gene or EP300 gene. Cross sectional research has indicated repetitive behaviour (RB) coupled with preserved social communication abilities in RTS; however, few studies have examined these characteristics longitudinally. In addition, there is limited research examining the causal mechanisms of RB in RTS. Two theories that have been proposed to explain RB are the executive dysfunction hypothesis and the theory that RB may serve to decrease anxiety. These theories were examined in this longitudinal questionnaire study.

Methods: Twenty-nine parents/carers of individuals with RTS (58.6% male; M_{age}=27.9 years) who participated in baseline assessments in 2007 (T1) completed a follow-up assessment in 2017 (T2; retention rate from 104 = 28%). Measures delivered at T1 and T2 included the Wessex Questionnaire, The Activity Questionnaire (TAQ), and the Social Communication Questionnaire (SCQ). Additional measures added at T2 included the Behaviour Rating Inventory of Executive Function – Preschool Version (BRIEF-P) and the Anxiety, Depression and Mood Scale (ADAMS).

Results: Impulsivity increased between T1 and T2 (Z = 0.25; p = .012). Increases in impulsivity were strongly associated with increases in RB (r = .60; p = .001) but not social or communication difficulties (ps > .05). Inhibition/self-control difficulties, as measured by the BRIEF-P, were associated with RB at T2 (r =.38, p = .044) and several mental health issues including hyperactivity (r = .75, p < .001), depression (r = .58. p = .001) and generalised anxiety (r = .63, p < .001). At T2, RB was only associated with compulsive behaviour on the ADAMS (r = .60, p = .001).

Conclusions: There is limited evidence for a direct link between anxiety and RB in RTS; however, difficulties with behavioural and/or emotional regulation may contribute to repetitive behaviour and mental health difficulties.

Keywords. Rubinstein-Taybi syndrome, repetitive behaviour, executive dysfunction, anxiety

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21: Concordance of the SCQ and ADOS in Identifying Autism Symptomatology in Genetic Syndrome Groups

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Background: Increased rates of autism spectrum disorder (ASD) occur in a number of genetic neurodevelopmental syndromes. However, profiles of autism symptomatology may differ from those typically associated with "idiopathic" ASD; ASD profiles also vary between syndromes. The Social Communication Questionnaire (SCQ) is a widely used screen to identify children at risk of ASD. The Autism Diagnostic Observation Schedule (ADOS and ADOS-2) is a semi-structured observational measure, often considered the "gold-standard" for aiding ASD diagnosis. The appropriateness of the SCQ and ADOS for identifying ASD in these groups remains unknown.

Methods: SCQ and ADOS data were collected for 231 participants (age 4 - 59 years) with genetic syndromes: Down (DS, n=68); Cornelia de Lange (CdLS, n=59); Rubinstein Taybi (RTS, n=28); Fragile X (FXS, n=51); Cri du Chat (CdCS, n=25). Vineland Adaptive Behavior Scales (VABS) scores were available for most (>90%) of the sample.

Results: Across the total sample, approximately 43% met criteria for ASD on both the SCQ and ADOS measures; 23% met criteria on neither. Of the remainder, 13% had scores at/above cut-off on the SCQ but not on the ADOS, and 21% scored positively on the ADOS but not on the SCQ. Sensitivity of the SCQ in relation to ADOS/ADOS-2 classifications was 68% and specificity 63%, both figures lower than those typically reported in studies of other autism cohorts. There was no consistent relationship between degree of concordance on these measures and participants' level of social, communication or daily living skills (as measured by the VABS). Agreement between SCQ and ADOS classifications (i.e., whether individuals met cut-off for ASD) also varied between syndrome groups, with agreement highest in the FXS and DS groups and lowest for individuals with CdCS.

Conclusions: Caution is required when using standard ASD assessment instruments to identify autism in individuals with specific genetic disorders.

Keywords: Autism, Down, Cornelia de Lange, Fragile X, Rubinstein Taybi, Cri du Chat

22: Visual Perception as a Window into the Nature of Autistic-Like Trait Expressions in Down Syndrome and Fragile X Syndrome

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Background: Children with fragile X syndrome (FXS) and Down syndrome (DS) are at increased risk of autistic-like impairment relative to the general population, yet debate is ongoing with regard to the precise nature of these comorbidities. There is research to suggest that these 'syndromic' forms of ASD manifest distinctly in terms of behavioural symptomatology; however, beyond this level of description, we know little of the nature of these comorbidities. Visuo-perceptual irregularities are well documented in isolated, often termed 'idiopathic', cases of Autism Spectrum Disorder (ASD). Visual search is one task domain in which visuo-spatial orienting manifests atypically in individuals with idiopathic ASD, often yielding enhanced performance outcomes – decreased target detection times - relative to NT controls. It remained to be seen whether behavioural manifestations of autistic-like impairment in children with FXS and DS were similarly characterised.

Methods: This study was a cross-syndrome study of visual search efficiency according to target detection latency data in children with idiopathic ASD (*n*=16), FXS (*n*=7) and DS (*n*=15) who were matched on chronological age, non-verbal intelligence and autistic trait severity.

Results: We found that children with idiopathic ASD outperformed their peers with FXS in terms of visual search efficiency, consistent with the notion of a syndrome-specific profile of autistic-like impairment in children with FXS according to underlying visuo-perceptual mechanism. No significant group differences were observed between idiopathic ASD and DS cases. Yet within the DS cohort, ASD comorbidity was associated with significantly decreased target detection times (improved search performance) suggesting a visuo-perceptual advantage similar to that which is considered a robust phenotypic marker of idiopathic ASD.

Conclusion: The results of this study illustrate the value of progressing beyond superficial behavioural indices of autistic-like impairment to examine, in a more fine-grained way, the neurocognitive features underpinning comorbid expressions of autistic-like deficit.

Keywords: Autism Spectrum Disorder, Down syndrome, Fragile X syndrome

23: How Does Genetic Diagnosis Influence Autism in Children with Intellectual Disability?

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Background: This study explored the relationship between genetic diagnosis and autism spectrum disorder (ASD) in children with intellectual disability (ID). To encompass multiple rare genetic diagnoses, participants were allocated to two groups defined by the functional annotations of causative variants: synaptic signalling (n=27) or chromatin regulation (n=23). We asked whether gene functional network predicts likelihood of ASD categorical diagnosis, ASD dimensional scores, emotional-behavioural characteristics co-occurring with ASD, or cognitive correlates of ASD.

Methods: Participants were recruited UK-wide via regional genetics centres. Standardised parent-report measures of adaptive ability, emotional-behavioural function and ASD traits were completed for all participants. We developed and implemented a new touchscreen-based, remote cognitive testing method (FarmApp), which yielded analysable data for 35 participants (ages 5 to 26 years, Vineland Adaptive Behaviour Composite scores 20 to 96).

Results: Functional network groups did not differ in categorical ASD likelihood. Item-level principal components analysis identified three ASD dimensions – flexibility, social understanding and social confidence – which did not differ between groups. Gene functional network predicted co-occurrence between ASD dimensions and non-ASD emotional-behavioural features. Within both groups, anxiety predicted flexibility. Within the synaptic signalling group, hyperactivity was associated with social understanding, whereas within the chromatin regulation group, inattention was associated with social understanding. FarmApp identified cognitive differences between functional network groups, not explained by IQ. Divergent associations between cognitive parameters and ASD dimensions were uncovered.

Conclusions: We find that genetic diagnosis does not enable direct predictions of ASD within childhood ID. Instead, genetic diagnosis can predict associations between ASD dimensions, non-ASD emotional-behavioural features, and cognitive abilities. This points toward alternative developmental mechanisms contributing to ASD, depending on underlying cause and neurobiological pathway.

Keywords: Autism, attention, memory, genetics, development, assessment

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24: Social Cognition Deficits in Adults with Triple X Syndrome

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Background: Triple X syndrome (47,XXX) is a genetic syndrome affecting 1 in 1000 females. Although girls with 47,XXX develop without major developmental disabilities, they tend to have mild developmental delays. Moreover, the full-scale intelligence quotient (FSIQ) in girls with 47,XXX is 15-20 points lower than in unaffected family members, and some girls with 47,XXX have social cognitive problems. Here, we present the first study regarding social responsiveness and emotion recognition in adults with 47,XXX.

Methods: In this cross-sectional study, 33 women with 47,XXX and 31 age-matched healthy women (mean age 32.9±13.1 vs. 34.8±13.7, p=0,57) were assessed using the adult informant version of the Social Responsiveness Scale (SRS-A) and the emotion recognition task (ERT). The ERT was used to assess the participants' ability to correctly identify six basic emotions (happiness, sadness, anger, disgust, fear, or surprise) in 180 facial expressions. The mean overall response latency (MORL) was also measured.

Results: Women with 47,XXX had higher scores (mean±SD) on all four SRS-A subscales compared to controls, including social awareness (17.5±9.2 vs. 9.8±7.1, p=0.0004), social communication (19.4±11.6 vs. 9.0±6.6, p<0.0001), social motivation (11.8±5.6 vs. 5.7±4.2, p<0.0001), and rigidity and repetitive behaviour (9.6±7.9 vs. 4.4±4.2, p=0.0017), as well as higher total SRS-A scores (58.3±31.3 vs. 28.8±20.0, p<0.0001) indicating a higher degree of impaired social cognition. Moreover, the ERT scores (which reflect the number of correctly identified emotions) were significantly lower in the women with 47,XXX compared to controls (100.8±20.5 vs. 115.2±16.0, p=0.0028), whereas MORL did not differ significantly (1831.3±1350.4 vs. 1768.6±768.6 ms, p=0.82).

Conclusion: Our results suggest that women with 47,XXX experience deficits in social cognitive abilities. Thus, routine assessment of social cognitive functioning should be considered in adults with triple X syndrome.

Keywords: Triple X syndrome, 47,XXX, social cognition

25: Genetics and Social Cognition: Developmental Changes in Emotion Recognition in Turner Syndrome

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Background: The accurate identification of facial affect is an essential component of social communication. The typical development of these skills follows a range of age-specific trajectories. Turner Syndrome (TS) is a sex chromosome aneuploidy (45,X) associated with autistic-like social adjustment difficulties that gain prominence during adolescence. Previous work has shown poor discrimination of fear and anger from other facial expressions. This study compares the developmental trajectories of facial recognition in young women with TS and age/sex matched controls aged 13-25.

Methods: Participants completed the Ekman-Friesen Pictures of Facial Affect test which assesses the ability to correctly identify 6 facial emotions: fear, anger, sadness, happiness, disgust and surprise. Normal population Z-scores (standardized for age/sex) are available from 6-60 years. 78 participants aged 13-25 with TS were recruited through the Turner Syndrome Support Society or specialist NHS clinics. Female normative data was acquired through data sharing from an earlier population-based study.

Results: 41 young women with TS aged 13-25 completed the task. Data from 299 females were available for the control sample. TS females identified fewer emotions correctly than age/sex matched population controls ($t(40)=-8.11$, $p<0.0001$). The TS group were overall relatively poorer at accurately recognising fear ($t(40)=-3.4$, $p=0.002$) and disgust ($t(40)=-12.16$, $p<0.0001$) than controls. There was a relative decline in accuracy in the TS group compared to controls, in the recognition of surprise, sadness, anger, fear and disgust between the ages of 13-25 years.

Discussion: The developmental trajectories of some aspects of facial emotion recognition are different in females with TS compared to age/sex matched controls. The ability accurately to identify facial expressions of fear and disgust deteriorates between 13-25 years compared to typical females. Increasingly impaired social cognition, observed in many females with TS, may contribute toward their experience of increasing social skills difficulties during adolescence.

Keywords: Turner syndrome, social skills, sex chromosome aneuploidy, social cognition, Ekman

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26: Social Cognition, Social Interaction and Social Behaviour in Cornelia de Lange, Fragile X and Rubinstein-Taybi Syndromes

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Background: The behavioural phenotype field lacks empirical studies that delineate causal pathways between gene disorders, cognition and behaviour. Subsequently, existing interventions aiming to improve social interaction skills and behaviours (social outcomes) lack specificity in which targeted skills (e.g. social cognition) predict particular behaviours within a genetic syndrome. This 'proof of principle' study explores the influence of early and later developing social cognitive abilities and syndrome group upon different directly observable social outcomes in genetic syndromes with characteristically divergent profiles of social behaviour; Cornelia de Lange (CdLS), fragile X (FXS) and Rubinstein-Taybi syndromes (RTS).

Methods: Thirty-six individuals with CdLS (Mage=12.42, SD=10.27), thirty-four with FXS (Mage=14.38, SD=11.87) and twenty-six with RTS (Mage=14.04, SD=12.64) participated in one of two batteries assessing either earlier (Early Social Cognition Scale; *ESCS*) or later developing (Theory-of-Mind Scale; *ToM*) social cognitive abilities, and the Autism Diagnostic Observation Schedule (ADOS-II). The frequency and quality of operationalised observable social interaction skills and behaviours were coded from ADOS-II recordings.

Results: Hierarchical linear regressions revealed greater *ESCS* scores predicted greater social enjoyment (R^2=.14, p<.01) and social motivation, (R_2=.09, p=.03), whereas greater ToMS scores predicted greater social enjoyment (R^2=.37, p<.01) and lower *ADOS-II* social affect severity scores (R^2=.19, p<.01), independent of chronological and non-verbal mental age. Syndrome group only independently predicted *ADOS-II* severity scores in individuals who took part in the *ToMS*. Correlations revealed no significant associations between *ToMS* score and *ADOS-II* scores within any of the syndrome groups.

Conclusions: Findings demonstrate that different social cognitive abilities predict different social outcomes in these syndromes and may highlight either developmental differences in the role of social cognition upon social outcomes, or that early and later developing social cognitive abilities are distinct constructs that influence social outcomes differently. The influence of syndrome on autism characteristics appears independent to the influence of later developing social cognition.

Keywords: Social cognition, sociability, genetic syndromes, Cornelia de Lange syndrome, fragile X syndrome, Rubinstein-Taybi syndrome

27 – TOM OPPÉ DISTINGUISHED LECTURE: Genes, Family, Time and Place: Challenges in Studying Behavioural Phenotypes

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Childhood onset neurodevelopmental disorders are highly heritable and have been the focus of in-depth genetic studies to 'find genes'. Depending on perspectives, that task has been either highly successful or not at all. In the case of autism for example large scale genetics studies have successfully identified rare chromosomal rearrangements and loss of function mutations that are likely to be causative for a small but significant minority of individuals. More broadly polygenic risk has been observed to increase risk across a range of neuropsychiatric conditions. Whole genome sequencing can now identify genomic sequence involved in gene regulation that may be influenced by the environment. The genomic era has produced a number of new challenges for behavioural phenotypes researchers. New rare syndromes have been described that require deep phenotyping and raise the hope of better cellular models for drug discovery using new technologies such as induced pluripotent stem cell models (IPSC). The completion of large scale genomics studies in autism and other neurodevelopmental conditions using categorical diagnoses has now turned the focus back to deeper phenotypes and cross-sectional studies are being replaced by longitudinal studies that can account for a range of possible influences on developmental phenotypes and trajectories. We remain challenged to integrate a multi-level understanding of behaviour. The question is whether novel technologies, big-data and the post-genome era will provide more answers or create more challenges.

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Abstracts for Research Symposium Day 2 *(in order of presentation)*

28 – KEYNOTE – THE GENETICS SOCIETY LECTURE: ASD Across Latin America: Diagnosis, Challenges, and Barriers to Care

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Globally, individuals with autism spectrum disorders (ASD) are amongst those with the highest percentage of unmet health care needs. Moreover, in most low-and-middle income countries, successful public policies for individuals with an ASD are largely lacking.

More than six million people with an ASD live in Latin America, a region where awareness, human resources, and infrastructure related to ASD are limited and unevenly distributed; however, in the past decade significant progress has been made in this region with several important studies being carried out, public policies developed and organizations established, including the Latin American Autism Spectrum Network (REAL) composed of researchers and clinicians from Argentina, Brazil, Chile, Uruguay, Venezuela, and the Dominican Republic. The REAL network has helped to strengthen ASD awareness and research collaborations in Latin America, its goal being to develop long-term policy solutions in the region.

In this presentation, we will contextualize the ASD scenario in Latin America from a public health perspective. The most recent scientific data available will be presented, including unpublished REAL network data. The current situation in Brazil, a country that accounts for almost one-third of the whole Latin America population, will be highlighted.

Keywords: Autism, Latin America, Epidemiology, Public Health, Barriers to Care.

29: Longitudinal Changes in Cognition in the LonDownS Cohort

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Background: The genetic association between Down syndrome (DS) and Alzheimer's disease (AD) is now well documented. However, questions remain concerning the clinical progression of AD in DS. Our previous cross-sectional work identified several cognitive measures in the LonDownS battery that were sensitive to differences in age and dementia-status in adults with DS. Here, we present longitudinal data from a sample of older adults (aged > 36 years) to determine which measures are most sensitive to change over time, in the presence and absence of cognitive decline at baseline.

Methods: Data from 117 adults with DS who completed the LonDownS Cognitive Battery twice, on average 23.7 (SD = 0.81) months apart, were compared using paired samples t-tests. The battery contains direct and informant-reported measures of general verbal and non-verbal abilities, memory, attention, executive function and motor control. Participants were stratified by baseline clinical status, supported by data from the Cambridge Examination for Mental Disorders of Older People with Down's Syndrome (CAMDEX): N = 47 were pre-clinical (no evidence of cognitive decline), N = 28 prodromal (evidence of early decline but no dementia diagnosis); N = 25 had a dementia diagnosis.

Results: Decline was seen in all groups, with different domains showing the largest effect sizes in each group. Pre-clinical group: paired-associates learning (first trial memory score) $t(36)=3.15$, $p=0.003$, $\eta^2=0.216$ and simple reaction time $t(32)=-2.63$, $p=0.013$, $\eta^2=0.177$; Prodromal group: verbal abilities $t(27)=4.33$, $p<0.001$, $\eta^2=0.409$ and every day skills $t(22)=-4.03$, $p=0.001$, $\eta^2=0.425$; Dementia group: orientation $t(23)=3.82$, $p=0.001$, $\eta^2=0.388$ and cognitive subscale from the Dementia Questionnaires for People with Learning Disabilities $t(22)=-4.29$, $p<0.001$, $\eta^2=0.456$.

Conclusions: Our tests of memory and attention show subtle early changes in pre-clinical adults with DS. Such measures show change before informant reports indicate any difference, highlighting the importance of direct cognitive assessments for adults with DS to monitor change.

Keywords: Down syndrome, dementia, Alzheimer's, cognition, memory

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30: Prevalence and Aetiology of Epileptic Seizures in Young People with 22q11.2 Deletion Syndrome and Relationships with Other Neurodevelopmental Disorders

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Background: 22q11.2 deletion syndrome (22q11.2DS) increases the risk of intellectual disability, psychopathology and epilepsy. The true prevalence of epilepsy in 22q11.2DS may be unknown however; previous estimates relied on historical medical record review and may have missed individuals with non-convulsive seizures (e.g. absences) not seen clinically. We aimed to conduct a first-hand, systematic assessment of epileptic seizures in 22q11.2DS, to better characterise their prevalence, aetiology and associations with other neurodevelopmental disorders (e.g. attention deficit/hyperactivity disorder, ADHD).

Methods: The parents of 108 deletion carriers (mean age = 13.6 years) and 60 unaffected control siblings (mean age = 13.1 years) completed a validated epilepsy screening questionnaire (ESQ). A second assessment with interview, electroencephalography and epileptologist review was conducted with a sub-sample (n=44). We explored other neurodevelopmental problems through parental questionnaire/interview and assessed IQ through neurocognitive testing with the child.

Results: Eleven percent of deletion carriers screened positive for an epilepsy diagnosis (controls 0%, p=0.004). However, 59.4% reported seizures or seizure-like symptoms without an epilepsy diagnosis (controls 13.3%, p <0.001). A fifth of deletion carriers reported febrile seizures (controls 0%, p<0.001). During the second assessment, one deletion carrier was newly diagnosed with epilepsy and two more with 'possible' absence seizures. A positive ESQ-screen was more likely in deletion carriers with a lower performance IQ (OR=0.96, p=0.018), ADHD (OR= 3.28, p=0.021), autism symptoms (OR=3.86, p=0.004) and motor problems (OR= 4.56, p=0.021).

Conclusion: Reports of seizures and seizure-like symptoms are common in 22q11.2DS, even when accounting for cases with diagnosed epilepsy. We show that these reports may be 'true' epileptic seizures in some cases, which are overlooked during routine clinical care. A propensity for seizures in 22q11.2DS is associated with risk of cognitive impairment, psychopathology and motor problems, which may suggest shared neurobiological risk pathways or deleterious effects of early-life seizures.

Keywords: 22q11.2 deletion syndrome, epilepsy, seizure, cognition, neurodevelopmental disorder, genetics

31: Correlation of Congenital Heart Disease Severity with Developmental Outcome in Patients with 22q11.2 Deletion Syndrome

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Background: Knowledge of medical co-morbidities conceivably influencing developmental outcomes in patients with 22q11.2 deletion syndrome (22q11.2DS) is important for providing anticipatory care and counselling families and healthcare providers alike. Congenital heart disease (CHD) is one of the most common related features. We examined the possible correlation between the presence and severity of CHD and neurodevelopmental outcomes, including Mean Full Scale IQ scores (MFSIQ) where available.

Methods: We retrospectively reviewed records on 1421 CHOP patients with 22q11.2DS. Those with formal cardiac evaluations (N=1102) were categorized from normal heart to simple, moderate or complex CHD. MFSIQs using the age appropriate Wechsler Intelligence Scale were analysed by subgroup. Age at achieving motor milestones and emergence of language were also examined.

Results: 64% had CHD including 42% classified as moderate or complex. 366 had MFSIQs, of whom 207 (57%) had CHD: 97 simple, 48 moderate, 62 complex. MFSIQ results: 76.22 (SD=13.46) (entire cohort), 76.86 (SD 12.70) (no CHD), 78.74 (SD= 11.95) (simple), 74.49 (SD= 15.85) (moderate), 72.42 (SD= 14.95) (complex). Z score analysis, using the overall mean to determine prevalence of significantly lower MFSIQ in any one classification, revealed no statistically significant difference in MFSIQ in subjects with any type of CHD versus those without. However, there was a trend towards lower MFSIQ in patients with moderate to complex CHD. We also noted mild but statistically significant delay in age at walking (median 17 months v. 14 months, p=0.002) among children with CHD but no delay in early language emergence between the two groups.

Conclusion: The presence or type of CHD does not appear to correlate significantly with developmental outcome in children with 22q11.2DS. However, the additive effect of co-morbidities, e.g. hypocalcemic seizures/ structural CNS differences, requires further exploration. Conversely, having 22q11.2DS alone may provide the best predictor of MFSIQ modified only by background genes.

Keywords: Chromosome, Microdeletion, 22q11.2, IQ, Heart, Comorbidity

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32 – KEYNOTE: SYNGAP1 Related Intellectual Disability: Understanding the Phenotype to Move Towards Trials

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Synaptic GTPase-activating protein 1 (SYNGAP1) is encoded by a gene located on chromosome 6p21.3. It is a major component of the post-synaptic density and plays an important role in synaptic development function, mainly through its effects on NMDA associated signalling pathways and AMPA receptor trafficking. Variants in SYNGAP1 were first shown to be associated with intellectual disability (ID) in humans in 2009 and the cases reported since that time have largely been found to display moderate to severe ID, epilepsy, autism and hyperactivity.

Interesting, our collaborators in Edinburgh, have shown that Syngap1 heterozygous mice similarities to mouse models of fragile X syndrome, both in terms of the convergence of biochemical pathways and their response to lovastatin, an inhibitor of the Ras-ERK1/2 pathway, raising the possibility that lovastatin may be an effective treatment for both conditions.

Parallel to these laboratory studies in Edinburgh we are currently conducting comparative studies of individuals with fragile X syndrome and those with pathogenic variants in SYNGAP1. These studies aim to determine whether there is also phenotypic convergence in humans and to pilot potential outcome measures and biomarkers of treatment response for future clinical trials of lovastatin in both conditions.

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33: The Relationship Between 47,XXY (Klinefelter syndrome), Autism Spectrum Traits (AST), and Early Hormonal Therapy (EHT)

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Background: 47,XXY (KS) is the most frequently occurring X&Y chromosomal variation (1:660), yet 75% remain unidentified. The social-cognitive phenotype of these boys includes language-based learning disorders, speech and motor delays, and executive dysfunction. Autism spectrum disorder (ASD) has been reported to be increased in 47,XXY, but this research has been confounded by many factors. This study investigated the incidence of Autism Spectrum Traits (AST) within the social-cognitive pathway and effects of early hormonal therapy (EHT) on AST in boys with 47,XXY.

Method: 74 boys with 47,XXY between 2-7 years underwent neurodevelopmental evaluations, including the Gilliam Autism Rating Scale, 2nd Edition (GARS-2); Social Responsiveness Scale, 2nd Edition (SRS-2); and Behavior Rating Inventory of Executive Function-Preschool (BRIEF-P). 30% received EHT, while 70% did not. EHT was administered based on paediatric endocrinologist's assessment of phallus size.

Results: On the GARS-2, boys in the EHT group showed significant improvement in social interaction compared to non-EHT group (*P*=.026). There was also a significant difference in the probability of ASD between the two (*P*=.038), where the non-EHT group had a 30.1% likelihood for AST compared to 13.6% in the EHT group. Positive effects of EHT were seen in the social cognition domain of the SRS-2 (*P*=.041) for the treated group. On the BRIEF-P, boys in the EHT group had greater emotional control (*P*=.029) and flexibility (*P*=.019).

Conclusion: This study provides further evidence that boys with 47,XXY present with an increased risk for disturbances on the social-pragmatic pathway. These results also suggest that when AST are suspected in undiagnosed young boys, genetic testing should be considered for 47,XXY to allow for targeted treatment opportunities, such as EHT, that may minimize effects as evidenced by this study. The origin of vulnerability warrants further investigation to identify those boys at greatest risks who need more specialized support.

Keywords: 47,XXY, Klinefelter syndrome, Autism, Early Hormonal Therapy, Social-pragmatic

34 – THE PAT HOWLIN PRIZE LECTURE: SOAR Study: New Approaches to Managing Social Skills Deficits in Turner Syndrome

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Background: Turner Syndrome (TS) is a sex chromosome aneuploidy (45,X) associated with social skill difficulties. 2016 Cincinnati TS clinical care guidelines recommend that the Program for the Education and Enrichment of Relational Skills (PEERS) social skills intervention is piloted. PEERS has primarily been used in face-to-face interventions with male adolescents with autism. This pilot project will also be the first to examine the feasibility and acceptability of the PEERS protocol online.

Methods: PEERS comprises 14 weekly lessons and runs two concurrent groups; one for participants and one for parents. Three face-to-face sessions were held at the start, middle and end of the program; all other sessions were conducted online using Adobe Connect Meetings.

The pilot used an uncontrolled study design with multiple-case tracking. The primary outcome measure (Social Competence with Peers; SCP) assessed social performance at 9 time-points (3x pre-intervention, 3x during intervention, 3x post-intervention). Secondary outcome measures assessed pre-post changes in social knowledge, anxiety, self-esteem, autistic symptomatology using standardised questionnaires and evaluated acceptability.

Results: PEERS was piloted with 7 young women with TS aged 17-20 with a verbal IQ above 70. At outcome social performance was significantly improved on the SCP by parent-report ($p=0.045$; $\delta=0.64$). Gains were maintained at follow-up. Significant improvements were observed in social knowledge ($p<0.0001$; $\delta=4.25$) and autistic symptomatology was reduced ($p=0.036$; $\delta=0.46$). No significant changes were found in standardised self-report measures of anxiety and self-esteem. 100% of participants rated PEERS as 'very helpful' and reported improvements in social ability.

Discussion: Online administration of PEERS was acceptable, feasible and effective; participants were highly motivated to improve their social functioning. Online delivery could substantially broaden the accessibility of social skills interventions in a cost-effective way to individuals with social communication deficits.

Keywords: Turner syndrome, social skills, sex chromosome aneuploidy, online intervention

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35 – THE LECLEZIO – DE VRIES LECTURE: Collaborating with Stakeholders on the Development of a "Flexible Scheduling" Early Intervention Approach Designed to Prevent Disabling Resistance to Change

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Background: Resistance to change is the emotional and behavioural response to altered expectations due to an insistence on sameness**.** Anxiety around changes expectations contributes to one of the core diagnostic domains of autism spectrum disorder (ASD), and is prevalent in other neurodevelopmental disorders, including Prader-Willi (PWS) and fragile-X syndromes (FXS). Such behavioural difficulties can be highly disabling for individuals and families. Evidence suggests that flexibility early in life may reduce later resistance by enhancing the development of cognitive processes contributing to the effective management of change. No existing approaches demonstrate efficacy in preventing such difficulties. This study aims to develop an intervention, which systematically increases variability in the activities of children at-risk of developing resistance to change behaviours.

Methods: An iterative user-centred design process was conducted with a Professional Advisory Network (n=12) and 44 families of children between 5-12 years (24 autism, 16 Prader-Willi, 4 fragile-X syndromes). Semi-structured interviews characterised groups with respect to support needs. Content analysis isolated design criteria, refined iteratively through focus groups. Features of the intervention tool were implemented at-home, across two testing periods, lasting 1 week and 4 weeks respectively.

Results: Feasibility of the intervention tool was assessed following both testing periods through semi-structured interviews and validated acceptability measures. Feasibility criteria include: the ability of families to integrate the approach, fidelity of remote implementation, sustained engagement, sensitivity of outcome measures, and rates of adverse events.

Conclusions: This web-based tool provides remote access to evidence-based principles to minimise change-related behaviour problems, while supporting parents to systematically encourage flexibility. This tool will allow future evaluation of the hypothesis that exposing children to more flexibility will prevent later difficulties with change through facilitating the development of the cognitive skills necessary to manage change effectively.

Keywords: rigidity, resistance to change, anxiety, cognitive flexibility, neurodevelopmental disorders

36 – KEYNOTE: Executive Function and Goal Directed Behaviour in People with Down Syndrome

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Down syndrome is the most common neurogenetic syndrome associated with intellectual disability, and many individuals with Down syndrome demonstrate pronounced difficulties with cognitive regulation and executive dysfunction throughout the lifespan. This presentation will focus on the development executive function in children with Down syndrome during the first decade of development. We will examine the links between executive function and outcomes in home, school, and community environments, and we will review recent findings regarding the earliest presentation of goal-directed foundations of cognitive regulation in infants with Down syndrome. The presentation will conclude with a discussion regarding implications for early intervention and future directions for this line of research.

Keywords: Down syndrome, executive function, behavioural phenotypes, early development, cognitive regulation

37: The Application of Attentional Control Theory for Anxiety in Cornelia de Lange Syndrome

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Background: DSM-5 anxiety symptomology and autism specific anxiety traits (e.g. Intolerance to Uncertainty [IU]) are prevalent in individuals with Cornelia de Lange syndrome (CdLS). Previous research has implicated executive functioning (EF) impairments in the emergence and maintenance of anxiety, specifically attention shifting and inhibition deficits (attention control theory). However, no research has explored whether this theory underpins anxiety in CdLS. In this study, associations between EF and subthreshold DSM-5 anxiety and IU were investigated.

Method: Caregivers of individuals with CdLS (***n***=24) completed direct and informant report measures of EF, subthreshold DSM-5 anxiety and IU. Individuals with fragile X syndrome (FXS) (***n***=28) comparable for level of ability, severity of autism symptomology and age were included as a contrast group.

Results: Subthreshold DSM-5 anxiety was present in both groups (CdLS=91.8%; FXS=100.0%) with high rates of comorbidity (CdLS=81.6%; FXS=88.9%). Autism specific anxiety was also prevalent (CdLS=43.8%, FXS=35.48% above cut-off), with specific difficulties for IU identified. Analyses showed presence of Social Anxiety, Specific Phobias and IU were associated with greater attention shifting deficits in CdLS (all ***p***<0.05), but not FXS. Additional analyses revealed greater scores for IU were associated with presence of Generalised Anxiety in both groups.

Discussion: Overall the findings suggest that in CdLS anxiety is a difficulty for a number of individuals and may be driven by attention shifting difficulties as proposed by attentional control theory. This was not observed for all anxiety types or for anxiety in FXS which may be driven by some other underlying mechanism. However, the association between Generalised Anxiety and IU is interesting and may suggest IU acts as a mediating factor between attention shifting deficits and Generalised Anxiety in CdLS. Understanding the cognitive underpinnings of anxiety in these groups has important implications for clinical practice to maximise the effectiveness of interventions.

Keywords: Cornelia de Lange syndrome, fragile X syndrome, anxiety, executive functioning, attentional control theory

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38: Mental Health Outcomes in Adults with Autism

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Background: It is widely accepted that mental health problems are more common in adults with autism spectrum disorder (ASD) than in the general population. However, the estimated prevalence of mental health difficulties in adults with ASD varies widely between studies due to methodological differences and method of obtaining and assigning mental health diagnoses. In addition, the majority of research focuses on early adulthood, or does not include individuals with comorbid intellectual disability.
Methods: The current study presents data from an ongoing longitudinal studying following a community sample of individuals with ASD from childhood to adulthood. Current mental health symptomology was collected from 80 participants (80% male; mean age = 33.8 years, range 26–44 years; 70% with comorbid ID), their family members, and/or professional carers, using the Structured Clinical Interview for DSM-5. The clinical information was reviewed by a panel, and consensus clinical diagnoses were assigned.
Results: Preliminary analyses suggest a high prevalence of comorbid mental health problems in adults with ASD. Information will be presented on rate and types of mental health problems, and childhood predictors of adult mental health problems will be explored.
Conclusion: The results will be discussed in relation to the need for interventions and supports for adults, along with the potential for targets for early intervention.

Keywords: autism, adults, mental health, longitudinal

39 – KEYNOTE: Restricted & Repetitive Behaviours: Impact, Associations and Uncertainties

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Restricted and repetitive behaviours (RRB) are common across a range of neurodevelopmental conditions and form part of the diagnostic criteria and behavioural phenotype of autism spectrum disorder. Despite the ubiquitous nature of RRB they are relatively under-researched and poorly understood. This presentation will consider the function, correlates and impact of RRB in autism. We will also explore evidence for the inter-relationship between RRB and a specific trans-diagnostic anxiety related mechanism: Intolerance of Uncertainty (IU). Evidence of how these constructs, interacting together, may underpin and maintain anxiety in autism will be presented. We will then consider a model of anxiety, which takes these interactions into account and consider the face validity of the model by reflecting on some first person accounts of RRB from autistic adolescents. Building on this RRB related outcomes from two recent intervention programmes will be presented, one targeting repetitive behaviours and one targeting intolerance of uncertainty. The talk will close with a consideration of the importance of cross syndrome comparisons in understanding the phenomenology of RRB.

Keywords: Restricted and repetitive behaviours, Autism, anxiety, uncertainty

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POSTER 1: Dissociated Recollection and Familiarity Components of Recognition Memory in Noonan Syndrome

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Background: Noonan syndrome (NS) is a genetic condition characterized by upregulated RAS–MAPK signaling, which is known to impact memory formation and consolidation, particularly if it is hippocampus dependent. Nevertheless, the profile of declarative long-term memory in individuals with NS has not been examined in depth. The aim of the present study was to investigate the contribution of recollection and familiarity to the recognition memory of children and adolescents with NS.

Methods: We compared 19 children and adolescents affected by NS with 22 typically developing (TD) children, matched for chronological age and non-verbal IQ, in two different experimental paradigms, to assess familiarity and recollection: a Process Dissociation Procedure (based on a verbal and visual memory task) and a Task Dissociation procedure (based on a visual memory task).

Results: Results of both experimental paradigms demonstrated reduced recollection and spared familiarity in participants with NS. To further investigate whether the observed impairment was related to verbal skills differences between groups, we carried out a second analysis on a selected group of 14 individuals with NS compared to 18 TD children matched for chronological age, non-verbal IQ and verbal comprehension. The analysis confirmed a dissociation of familiarity and recollection in the recognition memory of children and adolescents with NS which cannot be explained by intellectual disability or language deficits.

Conclusion: The impaired contribution of recollection, which is a hippocampal-dependent process, provides evidence to support the neurobiological hypothesis indicating the role of mutations impacting RAS–MAPK signaling in disrupting hippocampal memory formation and consolidation.

Keywords: Noonan Syndrome, Familiarity, Recollection, Declarative Memory, Hippocampal memory process

POSTER 2: ADHD and Type 1 Diabetes; the Comorbidity Increases Behavioural Challenges and May Affect Metabolic Control

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Background: Individuals with Type 1 diabetes (T1D) need lifelong treatment with injected insulin. The dose must be adjusted to current needs which differ according to food intake, physical activity, stress, fever etc. Optimal treatment of T1D requires good executive functions, which tend to be modest in individuals with attention deficit hyperactivity disorder (ADHD). Studies have reported poorer metabolic control in individuals with both ADHD and T1D than in those only T1D.

Methods: 14 children and adolescents with dual diagnosis (age 9 – 16 years) and their parents participated in different focus groups and discussed experiences of coping with ADHD and T1D.

Results: Parents: Both high and low blood sugar may affect ADHD-symptoms negatively. Impulsivity may result in the sudden ingestion of snacks and children forget to inject extra insulin. Decreased appetite because of Ritalin is a challenge for blood sugar control. The majority finds ADHD to be a more challenging disorder than T1D. Support from the child psychiatry is scare. Sleep in parents is commonly disrupted because they must wake up to monitor and adjust blood sugar levels in their children. A vast majority were diagnosed with ADHD before clinical onset of T1D.

Children/adolescents: Attention problems due to high or low blood sugar are different from ADHD symptoms. Some think that ADHD gives rise to more energy.

Conclusion: Most parents consider ADHD as a major challenge that complicates the treatment of T1D. Both high and low blood sugar may enhance symptoms of ADHD. When ADHD has not been diagnosed prior clinical onset T1D, there might be a risk for diagnostic over shadowing in individuals with poor metabolic control. More studies are needed.

Keywords: ADHD, type 1 diabetes

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POSTER 3: Autism Spectrum Disorder Symptomatology in SATB2-associated Syndrome

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Introduction: *SATB2* is located on chromosome 2q33.1. Deletions, duplications, translocations and point mutations involving the ***SATB2*** gene lead to a diagnosis of SATB2-associated syndrome; a recently defined disorder characterised by intellectual disability and absent/delayed speech. Although the physical characteristics of SATB2-associated syndrome are well documented (e.g. cleft palate, dental anomalies), the behavioural profile is less well delineated. Specifically, anecdotal reports of autism spectrum disorder (ASD) symptomatology and aggression in SATB2-associated syndrome require further exploration.

Methods: Caregivers of individuals with SATB2-associated syndrome (***n*** = 69; ***M*** age = 10.20 years, range = 1 – 36 years) completed online informant-report measures of ability, communication, behaviour, ASD symptomatology and mood-related states.

Results: Dental problems (96%), ear infections (67%) and gastrointestinal difficulties (59%) were prevalent in this group. Twenty-two individuals were non-verbal (less than 30 words/signs). High rates of physical aggression (78%), property destruction (46%) and self-injury (42%) were reported. Of the 59 individuals aged 4 years and older, 29 met clinical cut-off scores for ASD. The repetitive behaviour profile in SATB2-associated syndrome was characterised by stereotyped behaviours, attachment to particular people, attachment to objects and preference for routine. However, ASD symptomatology scores were comparatively lower in SATB2-associated syndrome than in an idiopathic ASD group from an existing dataset. Correlational analyses revealed positive associations between general anxiety scores and some repetitive behaviours in SATB2-associated syndrome (preference for routine: $r_{s=}.339$, $p = .004$).

Conclusion: Externalising behaviours were widely reported in children, adolescents and adults with SATB2-associated syndrome. However, ASD symptomatology was not convergent with the profile of repetitive behaviours and social communication deficits observed in idiopathic ASD. Rather, high levels of anxiety and pain-related behaviours may underlie some repetitive behaviours in SATB2-associated syndrome. The syndromic presentation of ASD characteristics in this group therefore warrants further investigation.

Keywords: SATB2-associated syndrome, autism spectrum disorder, behavioural phenotype, repetitive behaviour, anxiety, communication

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POSTER 4: The Development and Evaluation of the Emotional Outburst Questionnaire

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Background: Emotional outbursts are a component of the behavioural phenotypes of several genetic neurodevelopmental disorders and impact negatively on the lives of individuals and their families. Currently, emotional outburst measures are limited in their capacity to index change in severity, which is the desired outcome in intervention settings. They are also limited in their capacity to systematically describe characteristics of outbursts, which may indicate particular underlying pathways. By combining key beneficial aspects of interviews and questionnaires, the present study aimed to develop and validate the Emotional Outburst Questionnaire to overcome these limitations.

Methods: The Emotional Outburst Questionnaire was developed by reviewing existing measures. It was further refined by consultation with caregivers and professionals with relevant expertise. Online questionnaire responses were collected from over 300 caregivers of young people (6-25 years) with neurodevelopmental disorders, including a number of genetic syndromes. Item response theory was used to model a latent variable representing overall severity of temper outbursts. Cluster analysis was employed to generate different profiles of temper outburst characteristics.

Results: The outcomes of the item response theory analysis will be discussed in terms of the discriminatory power and difficulty of each item with respect to overall severity. Profiles generated from cluster analysis will be described in terms of differing temper outburst characteristics (e.g. frequency, behaviours, and antecedents).

Conclusion: The Emotional Outburst Questionnaire will facilitate future temper outburst research and associated interventions by reducing data collection time, whilst also offering more information than previous questionnaires. Items with the highest discriminatory power will be compiled into a short-form questionnaire for use as a severity screening tool in an intervention development setting. Different clusters of temper outburst characteristics may represent transdiagnostic behavioural phenotypes that are related to common neural, cognitive, and emotional underpinnings.

Keywords: Emotional outburst, questionnaire, item response theory, autism spectrum disorder, intellectual disability, behavioural phenotypes

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POSTER 5: Poster Empowering Families Through Technology: a Mobile-Health Project to Reduce the TAND Identification and Treatment Gap (TANDem)

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Background: Tuberous Sclerosis Complex (TSC) is a multi-system genetic disorder with a wide range of neuropsychiatric difficulties across different levels. They are the number one concern to families, but are highly under-identified and under-treated. To reduce this identification and treatment gap, we coined the term 'TAND' (TSC-associated neuropsychiatric disorders) and developed a 'TAND Checklist' for clinicians. We used TAND Checklist data in an international group of ~500 people with TSC and identified seven robust natural TAND clusters. Community-based participatory research next identified three themes– first, families liked the TAND Checklist, but wanted a version that they could complete for themselves; second, families were keen to have quantification of difficulties; third, families wanted the TAND Checklist on a digital platform such as smartphone or iPAD, and that the information entered should be connected to advice on next-step interventions for TAND.
Methods: The TANDem project will bring together TSC family and professional stakeholders, technology developers, global TSC stakeholders, and emerging TAND researchers around three main aims. First, development and validation of a quantified, self-complete TAND Checklist (TAND-SQ), designed as a Smartphone 'App'. Second, generation of consensus clinical guidelines for treatment of TAND clusters, to be incorporated into the TAND App. Third, development of a Global TAND Consortium through a range of networking, capacity-building and public engagement activities.
Results: In this presentation, we will outline the detailed protocol plan for the TANDem project. We will present the study rationale, methods, role of stakeholders, and will outline how the project will unfold over the next 4 years.
Conclusion: A successful project will transform the TAND landscape around the globe by empowering families through an easily accessible digital solution to identify their own TAND needs, and to provide them with consensus guidelines to prevent, treat and manage their TAND needs.

Keywords: Tuberous Sclerosis, TSC-associated neuropsychiatric disorders, behavioural phenotypes, technology, mobile health

POSTER 6: Sleep Disorders, Pain and Challenging Behaviour in Children with Smith-Magenis Syndrome (SMS) and Angelman Syndrome (AS)

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Background: Sleep disorders and challenging behaviour are common in individuals with intellectual disabilities. Pain and painful health conditions, whilst often under-identified and under-treated, are also purported to be frequent. There is emerging evidence of bi-directional relationships between painful health conditions, sleep disorders and challenging behaviour; these associations warrant further investigation. Smith-Magenis syndrome (SMS, caused by loss of material on chromosome 17p11.2) and Angelman syndrome (AS, most commonly caused by a deletion of the UBE3A gene), provide unique populations in which to investigate these putative associations, given the high prevalence of sleep disorders, painful health conditions and challenging behaviour in both groups.

Methods: Novel week-long actigraphy and daily pain and challenging behaviour ratings were collected for children with SMS (N=25) and AS (N=20). We used linear regressions to model the relationship between average total sleep time (TST, minutes), wake after sleep onset (WASO, minutes), sleep onset latency (SOL, minutes) and average pain and challenging behaviour ratings, across the study week. These analyses were conducted separately for children with SMS and AS. A multi-level modelling approach was also used to evaluate the temporal associations between each night's sleep and the subsequent day's pain and challenging behaviour ratings in these syndromes.

Results: In children with SMS, we observed a non-significant trend toward greater average WASO predicting a more severe average rating for challenging behaviour ($p=0.056$, $R^2=0.18$). The multi-level modelling between sleep quality, pain and challenging behaviour revealed temporal relationships between a number of these variables.

Discussion: The implications of these results for the assessment and treatment of sleep disorders and painful health conditions in interventions for challenging behaviour are discussed. Application of the methods used in this study, both assessment techniques and statistical analysis will be explored.

Keywords: Smith-Magenis syndrome, Angelman syndrome, sleep, challenging behaviour, pain, actigraphy

POSTER 7: A Linked Data Approach to Investigate the History of Rare Diseases and the Discovery of Their Genetic Cause

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Background: Rare diseases have been observed and documented since the ancient. Nevertheless, only since the development of molecular biology methods in the last century it was possible to identify and investigate their underlying genetic causes. In this study we collected and investigated first documentations of rare diseases and the discovery of their genetic cause and used this information for further analysis.

Methods: Data and information about rare genetic diseases, their causative genes and literature information about the first publication were collected from OMIM, Whonamedit, PubMed, and Google scholar. The dataset was constructed and harmonised in a spreadsheet and as machine-readable RDF nanopublication. The data is available in a Figshare data collection. The acquired data identifiers were then used to harvest information from other resources like Wikidata, DisGeNET, and Orphanet.

Results: According to underlying data, the description of rare genetic diseases started in 1788 with osteogenesis imperfecta. The first discovery of a causative gene was in 1967 with the gene causing Lesch-Nyhan syndrome. Investigating the timeline, the discovery rate of genes is linked to developments in molecular biology techniques while first descriptions of rare diseases follow the general trends in publication numbers. Analysis of citation scores reveals that there are rare but highly researched diseases like Rett syndrome, ALS, and rare genetic causes of common diseases like Alzheimer's and Parkinson's disease, and truly neglected diseases. Using identifier mapping, made available by DisGeNET, further information like disease prevalence data from ORPHANET, preferred publication journals from Wikidata, and disease super classes from DisGeNET could be acquired.

Conclusion: The creation of this dataset is an example how linking data can give benefit and allows drawing new conclusions – e.g. about the documentation of rare diseases and their causative genes. A crucial part is identifier and entity mapping, which allows to link data across different resources.

Keywords: rare diseases, genetic diseases, genotype-phenotype, history of science, research infrastructure, data science

POSTER 8: The Pathways of Rett Syndrome Revealed by Different Methods for Pathway and Network Analysis

***Ehrhart F.*[1,2], *Kutmon M.*[1,3], *Bahram Sangani N.*[1,2], *Miller R.A.*[1], *Eijssen L.M.T.*[1], *Slenter D.N.*[1], *Willighagen E.L.*[1], *Coort S.L.*[1], *Evelo C.T.*[1], *Curfs L.M.G.*[2]**

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Background: Rett syndrome is a rare genetic disorder caused by a loss of function mutation in MECP2, an important regulator of gene expression especially, but not only, in neurons. Due to the multi-functionality of MECP2 there are many downstream pathways which are interesting for understanding the pathophysiology of Rett syndrome, and allowing a search for drug targets. Using omics data and analysing it in terms of biological pathways and networks allows a holistic view of the influence of MECP2. In the past years several methods have been developed, which we will demonstrate here.

Methods: Transcriptomics microarray data was collected from several previously published studies of which differentially expressed gene lists were extracted. Overrepresentation analysis of biological pathways was done in PathVisio software using the pathway database WikiPathways (including Reactome pathways). For active module analysis, first, the whole WikiPathways database was used to construct one large network and, second, active modules based on differently expressed genes were identified using the Cytoscape app jActiveModules. For comparison, gene ontology analysis was performed using GO_Elite software.

Results: The integrative approach, using different pathway and network analysis methods to analyse transcriptomics datasets, revealed several downstream pathways of Rett syndrome. The different methods showed a clear overlap in ability to identify disease affected processes in inflammation, neuronal development, neuronal function, and translation. Pathway analysis was less effective to show affected processes in translation, which were identified clearly by gene ontology and active modules analysis. This is possibly due to a limited number of available pathways focussing on translation related processes.

Conclusion: Although the details of identified pathways and active modules in the networks differed in each method used, the different methods showed a significant overlap in identification of pathways and processes which are clearly linked to the Rett syndrome phenotype.

Keywords: Rett syndrome, pathway analysis, active modules, gene ontology, network analysis, transcriptomics data

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POSTER 9: Influences of Social Cognition and Reward Processing on Autism Symptoms in Prader-Willi Syndrome

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Introduction: Prader-Willi Syndrome (PWS) is a neurogenetic syndrome caused by the loss of expression of paternally expressed genes from the paternally inherited copy of chr15q11 – 13. PWS is characterised by the onset of hyperphagia in childhood leading to morbid obesity. Hyperphagia in PWS is considered to be due to an impaired satiety response and an increased reward value of food. Autism Spectrum disorder (ASD) symptoms, including atypical social cognition, are prevalent in PWS cases and intriguingly, appear to increase in PWS across childhood. The social motivation theory of ASD proposes that social cognition impairments are largely driven by social motivational deficits. We hypothesise that the onset of hyperphagia may reduce the reward value of social stimuli and contribute to the relative increase of ASD symptoms seen in later childhood in PWS cases.
Methods: We will phenotype ASD symptoms and hyperphagic behaviour in individuals with PWS (n=60, age 4 – 40y) and age matched controls. To test if reduced valence of social reward underpins ASD symptoms in PWS, we will characterise social cognition comprehensively using a battery of accessible and validated eye-tracking paradigms. To test the relationship between reward valence for social cognition and hyperphagia, we will compare reward processing for food stimuli; social stimuli; and non-food/non-social stimuli. A dynamic preferential looking paradigm will be used to investigate differences in attentional bias between PWS cases and controls in hungry and satiated conditions.
Results: Data collection for this study is on- going. We will present preliminary analysis from the initial recruitment phase of performance of PWS cases (N=10) and controls (N=10) on the eye=tracking batteries.
Conclusion: The results of this study will help us understand if reduced valence of social reward underpins ASD symptoms in PWS and if it is related to the onset of hyperphagia.

Keywords: Prader-Willi Syndrome, Social Cognition, Reward Processing, Eye-Tracking

POSTER 10: Communication Profile in Persons with Angelman Syndrome from Spain and Portugal

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Background: Angelman syndrome (AS) is a severe neurodevelopmental disorder with an estimated prevalence of 1 in 20.000 – 30.000 new-borns. It is caused by the lack of expression of maternally inherited imprinted genes of chromosome 15q11-q13. The AS has a characteristic phenotype including severe intellectual disability, severe speech impairment, epilepsy, happy demeanour, excessive laughter, easily excitable personality, hyperactivity and fascination with water.

Methods: Our aim was to explore the levels of language and communication in 29 and 13 individuals with AS from Spain and Portugal respectively, aged between 5 – 45 years, using the MacArthur Communicative Development Inventory (CDI – Infant Form) in collaboration with the associations of persons with AS from both countries.

Results and Conclusion: The results showed specific communication and language characteristics in persons with AS in words and gestures. The vocabulary comprehension is better than production, with better performance in semantic categories of: games and routines, people, body parts, toys, food and drinks, clothing, furniture and rooms. The use of deictic gestures predominates and highlight: extends arm to show something, reaches out and gives you a toy or some object, extends their arms upward to signal a wish to be picked up. The differences by the genetic cause showed that persons with AS deletion performed worse than those from non-deletion group. Picture cards and natural gestures were preferably used for communication. Significant differences between countries, but not by the education level of the caregiver, were found. This intercultural study provides more knowledge about behavioural phenotypes of communication in persons with AS that could lead to an improvement in therapy intervention and multimodal methods of communication.

Keywords: Angelman Syndrome, Severe Intellectual Disability, Communication Profile, Behavioural Phenotypes, intercultural studies

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POSTER 11: Psychiatric Assessment in Phelan-McDermid Syndrome (22q13 Deletion Syndrome)

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Background: Phelan-McDermid Syndrome (PHMDS)/22q13.3 deletion syndrome is a rare genetic disorder associated with Autism Spectrum Disorder (ASD) and Intellectual Disability (ID). There are reports of PHMDS co-occurring with psychiatric disorders, particularly bipolar disorder, but little is known about the assessment of such disorders in PHMDS.

Method: A case study describing the assessment of a single male patient referred with periods of unrest and challenging behaviour to a specialised hospital ward for individuals with ASD / ID. We explored whether approaches to psychiatric assessment in ASD/ID may be applicable in PHMDS and whether any adjustments were necessary.

Results: The patient was diagnosed with Bipolar disorder type 1. The standardised assessment instruments used will be presented. The strategies employed in the psychiatric assessment of this individual with PHMDS ASD and ID was similar to the strategies utilized in the assessment of individuals with ASD and ID generally.

Conclusions: Findings indicate that strategies employed in psychiatric assessment in individuals with ASD and ID may be utilized in individuals with PHMDS with little or no adjustment. Developing more systematic approaches to psychiatric assessment in individuals with PHMDS is important, both for further research and in the clinic. The findings highlight the importance of general knowledge of ASD and ID in order to identify psychiatric disorders in individuals with rare genetic conditions such as PHMDS. As yet, the prevalence of psychiatric disorder in PHMDS is unknown, and systematic assessment strategies are important to obtain accurate data on the risk of mental health problems, particularly bipolar disorder, in this population.

Keywords: Phelan-McDermid Syndrome; 22q13.3 deletion syndrome; psychiatric disorder; bipolar disorder; Autism; assessment

POSTER 12: The Development and Psychometric Properties of the Angelman Syndrome Behavioural Scale

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Background: Angelman Syndrome (AS) is a rare neurodevelopmental disorder affecting 1 in 15,000 to 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 longitudinal studies to advance research and therapeutics. This study describes findings on behaviour.

Methods: A total of 184 caregivers completed a 29-item questionnaire about their child/ adult's behaviour. A maximum likelihood exploratory factor analysis with oblique rotation was conducted on the scale, resulting in a 7-factor solution. Relationships between age, phenotype, and behaviour were explored.

Results: Factors included: Behaviour dysregulation (e.g. impulsivity, biting; 6 items, α=.780), Anxiety (e.g. agitation in new situations, fear of strangers; 5 items, α=.810), Spontaneous laughing/ smiling (3 items, α=.836), Self injury (e.g., self hitting; 3 items, α=.703), Appropriate laughing/ smiling (2 items, α=.644), Repetitive behaviours (e.g. focal movements; 3 items, α=.642), and Impulsivity/ hyperactivity (2 items, α=.512). Moderate correlations were observed between self injury, anxiety and behaviour dysregulation (*r spearman range* = .290-.411), and spontaneous laughter/smiling and repetitive behaviour (*r spearman* = .407). Behaviour dysregulation was more common in individuals aged over 5 years compared to younger individuals (*Kruskal-Wallis* = 39.394, $p < .001$, $d = .986$). Carers of individuals with a chromosome deletion noted higher levels of spontaneous laughter/ smiling (*Mann-Whitney U* = 2,223.000, $p = .009$, $d = .030$). By contrast, individuals with other diagnoses exhibited higher levels of anxiety (*Mann-Whitney U* = 2,730.000, $p = .021$, $d = .374$), self-injury (*Mann-Whitney U* = 2,589.000, $p = .044$, $d = .292$) and behaviour dysregulation (*Mann-Whitney U* = 2,870.000, $p = .004$, $d = .474$).

Conclusion: Psychometric properties were acceptable for four scales, and suggested higher levels of behavioural problems were associated with older age and genotype. Further revisions could expand the scale and improve reliability.

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POSTER 13: Common Behavioural Features of Autism, Fragile X Syndrome and 22q.11.2 Deletion Syndrome

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Background: Autism Spectrum Disorder (ASD), Fragile X Syndrome (FXS) and 22q.11.2 deletion syndrome (22q.11.2DS) are neurodevelopmental conditions characterized by neuropsychological and behavioural problems. It has been suggested that dysregulation of the endocannabinoid pathways in the central nervous system may underlie the socio-behavioural deficits seen in ASD and FXS. The most common behavioural problem across all conditions are anxiety related symptoms which may manifest in varying severities of social avoidance, aggression, irritability, attention deficits, stereotypy, poor communication and social unresponsiveness. We aim to evaluate the common behavioural problems consistent across these conditions with specific attention to role that cannabidiol (CBD) may play to ameliorate these symptoms.

Methods: A literature review was conducted (from the last decade) of behavioural symptoms in autism, FXS and 22q.11.2DS characterizing the most common behavioural complaints from parents and caregivers. The clinical benefit of CBD in the treatment of anxiety symptoms is also summarized.

Results: Anxiety related concerns are high in ASD with 11 – 84% of children experiencing some degree of anxiety. Co-morbid anxiety disorders can be broad ranging and associated with acting out behaviours such as aggression/irritability or isolation from same age peers. In FXS, the most frequent caregiver-reported behaviours were: seeks isolation from others, lack of interaction and aggressive to others. Children with 22q.11.2DS are often withdrawn and have difficulty with social interaction and anxiety. CBD has demonstrated benefit in reducing social anxiety in man and in animal models of anxiety.

Conclusions: Anxiety and the constellation of socio-behavioural-related symptoms are common across ASD, FXS and 22q.11.2DS. These are often considered the most bothersome symptoms for caregivers to manage. CBD has been shown to improve anxiety and may prove to be effective across the spectrum of behavioural problems in these conditions.

Keywords: Autism, Fragile X Syndrome, 22q.11.2 Deletion Syndrome, Anxiety, Cannabidiol

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POSTER 14: Further Delineation of Phenotypes Related to Integral Cohesin Structural Protein RAD21

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Background: Aberrations in RAD21 (RAD21 Cohesin Complex Component) are associated with clinical phenotypes overlapping with Cornelia de Lange Syndrome (CdLS). Although RAD21 variants seem to lead to a relatively mild CdLS phenotype, knowledge is based on only a small number of individuals. We aimed to provide a complete overview of RAD21 variants reported thus far, and delineate the phenotype with special attention to cognition and behaviour.

Methods: Using international inquiry, literature and database search, we identified 53 RAD21 cases, including 21 new index cases. With a dedicated questionnaire, extensive and updated data was obtained for deep phenotyping in a core cohort of 29 patients (24 sequence variants, 5 small microdeletions). Phenotypes were compared to cohorts of 67 patients with NIPBL (Nipped-B-like protein) and 51 patients with SMC1A (Structural Maintenance Of Chromosomes 1A) variants. In silico analyses of mutation effects and genotype-phenotype relationships were investigated.

Results: All 29 patients in the core cohort had sufficient features of CdLS to warrant molecular testing. Thirteen met clinical criteria for classical, and 12 for non-classical CdLS. Somatic, cognitive and behavioural problems were markedly less prevalent and less severe in the RAD21 cohort. Importantly, little self-injurious behaviour (n=1, NIPBL: 77%) and no major limb malformations were found. Cognitive functioning tended to be normal to only mildly impaired, but even without intellectual disability patients tend to have subtle problems in development, cognition and behaviour. In contrast to NIPBL and SMC1A patients, eventually all RAD21 patients learn to walk and communicate verbally. Behavioural and psychiatric problems (44%) include anxiety, autism spectrum disorder and attention deficit hyperactivity disorder. Exploration of six families demonstrated marked intrafamilial variation. Genotype-phenotype analyses will be presented at the meeting.

Conclusions: The data presented in this comprehensive overview should be of benefit to physicians when counselling families with affected members with a RAD21 variation.

Keywords: RAD21 (RAD21 Cohesin Complex Component), Cornelia de Lange Syndrome, Deep phenotyping, Genotype-phenotype correlations, cognitive functioning, behaviour

POSTER 15: Mood, Anxiety Disorders and Problem Behaviours in Children and Adolescents with Fragile X Syndrome

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Background: Children and adolescents with Fragile X Syndrome (FXS) are more likely to develop mood, anxiety and behavioural problems compared to the general population. This study aimed to systematically review the literature investigating the prevalence of these problems in children and young people with FXS.

Methods: We explored manuscripts for children and adolescents under the age of 18 with FXS for the prevalence of these problems.

Results: The prevalence rates of mood, anxiety disorders and problem behaviours in children and adolescents with FXS were substantial and varied markedly across different studies.

Conclusion: Several aspects including developmental factors, gender and other comorbidities need to be considered when evaluating anxiety and mood disorders, and problem behaviours, in individuals with FXS

Keywords: Fragile X Syndrome, mood, anxiety, behaviour

POSTER 16: The Incidence of Anxiety Symptoms in Toddlers and School-Age Boys with 47,XXY (Klinefelter Syndrome) and the Potential Impact of Hormonal Replacement Therapy (HRT)

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Background: 47,XXY (KS) is the most common X&Y chromosomal variation (1:660 males), but 75% remain undiagnosed. The phenotype includes accelerated height, language-based learning disorders, motor delays, and behavioural problems. Past studies demonstrated hormonal replacement therapy (HRT) may improve the neurodevelopment of boys with 47,XXY. Incidences of anxiety-related symptoms in 47,XXY and the potential impact of HRT have not been well investigated.

Methods: Parents of 48 toddlers and 45 school-age boys with 47,XXY completed Child Behavior Checklists. 58.3% of toddlers and 64.4% of school-age boys received HRT. The rest were untreated (non-HRT). HRT was based on an evaluation by a paediatric endocrinologist. Biostatistics was completed to analyse differences between HRT and non-HRT groups.

Results: 10% of non-HRT toddlers showed clinical symptoms (above 92nd percentile) in anxious/depressed, somatic complaints, and withdrawn while 15% had internalizing problems. Only 3.57% of HRT-treated toddlers had clinical symptoms in withdrawn, internalizing, and externalizing problems. HRT-toddlers had less symptoms in affective problems compared to non-HRT ($t(46) = 2.18$, $P=0.017$). Non-HRT school-age boys were above the 92nd percentile in somatic complaints (31.25%), internalizing (50%), externalizing (43.75%), affective (37.5%) and anxiety problems (25%). HRT-boys had significantly fewer symptoms but showed an elevation in internalizing (34.5%), externalizing (27.5%), affective (24%) and anxiety problems (24%). HRT-boys had less symptoms in somatic ($t(43) = 1.9$, $P=0.03$), thought ($t(43) = 2.05$, $P=0.023$) and social problems ($t(43) = 1.96$, $P=0.028$).

Conclusion: Our findings demonstrate anxiety and internalizing behaviours may be a penetrant aspect of the 47,XXY phenotype beginning as early as 3 years of age and increasing with age. This research supports the potential positive effect of HRT on neurodevelopment in boys with 47,XXY with less reported symptoms in HRT-boys at both ages. Further studies examining the impact of HRT on anxiety at different ages to develop more personalized and precise treatments are needed.

Keywords: Klinefelter syndrome, 47,XXY, Anxiety, Behaviour, Phenotype, Treatment

POSTER 17: Age Related Changes in Behavioural and Emotional Problems in Smith-Magenis Syndrome

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Background: Smith–Magenis syndrome (SMS) is a rare, complex genetic syndrome caused by an interstitial deletion of chromosome 17p11.2 or a mutation in the retinoic acid-induced 1 (RAI1) gene. The aim of this study was to investigate the Developmental Behaviour Checklist (DBC) profile of persons with SMS and how this relates to measures of ASD symptoms, adaptive level and age.

Method: Parents of 28 persons with SMS aged between 5 and 50 years participated in this study, 11 of the persons with SMS were above the age of 18 at the time of the study. A total of 12 came from Sweden and 16 were from Norway. The mean age was 17.5 with a range from 5.2 – 50.5.

Results: The DBC results from 28 persons with SMS were analysed. DBC-Total scores are reduced with age, but they still show a mean that is clearly above the cut-off of 46. The differences between the age groups <9 years and 9 – 17 years (p=0.024) and between the age groups <9 years and >18 years (p=0.007) are significant. There is no significant difference between the age group 9 – 18 years and >18 years. There are significant differences between the youngest and oldest age groups in all but the Communication Disturbance and Social Relating sub-scales. Between the youngest and middle groups, there are no significant differences when we examine p values. There is a large effect between the youngest and the middle group in the Anxiety sub-scale when we use Cohen's D. Between the middle group and the oldest group, the only significant difference is in the Disruptive/ Antisocial sub-scale.

Conclusion: We found a significant decrease in behavioural and emotional problems with age in SMS. Adaptive skills were related to the behavioural problems, this need to be further explored.

Keywords: Smith-Magenis syndrome, rare disorders, behaviour and emotional problems, adapted behaviour

POSTER 18: Digital Interventions for Emotion Regulation and Social Cognition in Children and Adolescents with Neurodevelopmental Disorders: A Systematic Literature Review

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Background: The experience of relatedness and belonging with peers throughout adolescence is a significant protective factor for psychological wellbeing. Universally, adolescents with good emotion regulation (ER) and social cognition (SC) skills are more likely to report high quality social networks. Behavioural phenotypes linked to several genetic neurodevelopmental disorders (NDDs) comprise deficits in ER and SC. Such deficits can be associated with poor social functioning. Hence, there is a need to promote these vital skills at an early age to support optimal psychological wellbeing across the lifespan. Digital technologies may overcome some of the barriers to uptake and maintenance of psychological interventions for individuals with NDDs. Here we describe a systematic literature review aiming to elucidate the current impact of ER and SC digital interventions in children and adolescents with NDDs.

Methods: PRISMA guidelines were followed. Papers that described an intervention targeting ER or SC, using digital technology, with typically or atypically developing child and adolescent populations were included. Grey literature and hand searching identified further papers. Following double independent screening, data extraction and systematic risk of bias rating, papers were clustered by skill, intervention and population.

Results: Of the 65 studies included, 66% targeted children and adolescents with NDD but none specifically targeted those with genetic syndromes. Across cluster patterns included small sample size, moderate to long intervention and high level of evidence when the caregiver was integrated in the intervention. For NDD populations, the strongest evidence is available for device-based interventions (e.g. Google Glasses) targeting SC in ASD populations. This contrasts to typical populations where the strongest evidence was available for digital game interventions targeting ER.

Conclusion: There is huge potential for ER and SC digital intervention research to inform on challenges surrounding behavioural phenotypes of numerous genetic NDDs. However, greater sub-discipline integration of methods and approaches is required.

Keywords: neurodevelopmental disorder, emotion regulation, social cognition, digital, intervention, adolescent.

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POSTER 19: Parent-Reported Positive Character Traits in Individuals with Angelman and 22q11.2 Deletion Syndromes

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Background: The majority of research with individuals with rare genetic disorders focuses upon difficulties, such as severity of intellectual disability, communication impairment, or level of challenging behaviours. Whilst this is important, and has increased our understanding of profiles and trajectories for individuals with rare genetic syndromes, this deficit focus has resulted in a lack of research exploring positive attributes. There also remains a lack of research exploring factors that may influence the identification of such positive attributes.

Method: Parents of 82 individuals with Angelman (AS; n=39), 22q11.2 deletion syndrome (n=17) and other syndromes (n=26) completed an online survey. Parents completed the Assessment Scale for Positive Character Traits-Developmental Disabilities (ASPeCT-DD) which asks about their child's (a) positive relations, (b) active coping, (c) acceptance coping, and (d) positive outlook. Additionally, parents completed a demographic questionnaire, the WESSEX and the Challenging Behaviour Questionnaire.

Results: Although there were no significant differences in the ASPECT-DD total or subscale scores between diagnostic groups, syndrome-specific profiles were noted at item level. The item with the highest score for AS group was "*This person seems to enjoy life and is thankful for life's simple pleasures*" ($\bar{x}$=4.08) and for the 22q11.2 group was "*I think this person is courageous*" ($\bar{x}$=3.76). ASPECT-DD scores were not correlated with child age, but ASPECT-DD total, positive relations positive coping and active coping subscales were positively correlated with the Wessex self-help scores ($p<.05$). Children showing self-injurious behaviour had significantly lower scores on only one ASPECT-DD subscale; active coping ($p<.05$).

Conclusions: Every individual possesses a range of character strengths and traits; this is no less true of individuals with rare genetic syndromes. Findings suggest the profile of strengths may be associated with both individual factors as well as genetic diagnosis and highlight the importance of encouraging parents to identify such strengths in their children.

Keywords: Strength, Personality, Positive, Syndrome, Behaviour

POSTER 20: Psychological Mechanisms Underlying Anxiety in Adolescents and Adults with Williams Syndrome.

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Background: Anxiety is a highly prevalent psychopathological disorder in individuals with Williams syndrome (WS). However, little is known about the neurocognitive mechanisms that underlie anxiety development. This study examined two potentially related cognitive mechanisms, an intolerance of uncertainty (IoU) and executive functioning deficits. Repetitive behaviour was also investigated due to the identified relationship between these behaviours, IoU and anxiety in other neurodevelopmental disorders.

Method: 34 caregivers of adolescents and adults with WS participated in the study (mean age: 30.00, SD: 12.41, range: 13 – 58, 13 male). Mechanisms were explored and compared utilising two methods of anxiety assessment, the Kiddie Schedule of Affective Disorders–Present and Lifetime Version (KSADS-PL) and the Spence Children's Anxiety Scale–Parent Version (SCAS-P). The p-value was set at .01.

Results: Correlations between the KSADS and SCAS total score approached significance (Rpb=.42, p=.015). A relationship between IoU and anxiety was identified using both the SCAS-P (r=.66, p<.0001), and the KSADS-PL (t(28)=-2.52, p=.018), with those scoring higher for IoU scoring higher on anxiety measures. Both measures also produced similar results in relation to repetitive behaviour, finding limited associations with anxiety, despite repetitive behaviour and IoU being independently linked (rs=.60, p<.0001). Discrepancies between anxiety measures were identified for executive functioning, with limited associations found with the KSADS-PL, although several correlations were identified between executive functioning deficits and the SCAS-P, including for shifting attention (r=.60, p<.0001) and behavioural regulation (r=.67, p<.0001).

Discussion: IoU may be a neurocognitive mechanism underlying anxiety for individuals with WS, and whilst repetitive behaviour may be linked with IoU independently, it is not associated with anxiety unlike in some other neurodevelopmental disorders. Executive functioning deficits may be associated with anxiety, although the different assessment measures produced different results, compromising the conclusions that can be drawn and this requires further investigation.

Keywords: Williams syndrome, anxiety, psychopathology, intolerance of uncertainty, executive functioning, repetitive behaviour

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POSTER 21: Content Validity of the ABC-CFXS and Subscales in Fragile X Syndrome

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Background: Fragile X Syndrome (FXS) is a genetic condition caused by a mutation in the Fragile X mental retardation 1 gene. The core behavioural symptoms of FXS include anxiety, social avoidance, irritability, and social unresponsiveness/lethargy. The goal of this study was to establish the content validity of the Aberrant Behavior Checklist-Community ($ABC\text{-}C_{FXS}$), a validated assessment commonly used to evaluate behavioural symptoms in FXS, by determining the accuracy by which it captures the caregiver perspective of FXS symptoms and behaviours.

Methods: Ten caregivers of children with FXS were recruited via the National Fragile X Foundation in the United States. Caregivers participated in phone interviews conducted by a trained interviewer using a semi-structured interview guide. Thematic analysis of the transcripts was conducted to examine patterns in the data.

Results: All caregivers were mothers of children with FXS (mean age: 38 and 10 years, respectively) and 80% reported that their child's doctor described their FXS as moderate or severe. The most frequent behavioural symptoms related to FXS were: seeks isolation from others (70%), lack of interaction (60%), and aggressive to others (60%). Socially avoidant behaviours such as seeks isolation from others [70%], prefers to be alone [40%], and prefers solitary activities [20%]) were frequently reported and are reflective of the items on the Social Avoidance subscale. Similarly, aspects of misbehaviour and irritability frequently reported (aggressive to others [60%], irritability [50%], temper tantrums/outbursts [50%], screaming/yelling inappropriately [40%], harming others [40%], and stubbornness [30%]) mapped to the Irritability subscale. Lack of interaction (60%) and lack of attention (50%) mapped to the Socially Unresponsive/Lethargic subscale.

Conclusions: This research provides evidence supporting the content validity of the $ABC\text{-}C_{FXS}$ subscales Social Avoidance, Irritability, and Socially Unresponsive/Lethargic in FXS. Moreover, it further validates social avoidance as a core behavioural symptom from the perspective of caregivers of children with FXS

Keywords: Intellectual and Developmental Disabilities; Fragile X Syndrome; Aberrant Behavior Checklist-Community; Content Validity; Caregiver

POSTER 22: Hormonal Replacement Therapy (HRT) and its Potential Positive Influence on Working Memory (WM) Capabilities in Boys with 47,XXY (Klinefelter syndrome)

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Background: 47,XXY is the most commonly occurring X and Y chromosomal variation (1:660), yet 25% remain undiagnosed. Neuroimaging studies have shown frontal lobe deficits, leading to weakness in executive functioning skills, including working memory (WM). Previous studies revealed that hormonal replacement therapy (HRT) may significantly improve neurodevelopment, speech and language, intellectual functioning, and behavioural problems in 47,XXY. HRT has yet to be investigated on WM outcomes.

Method: 111 boys with 47,XXY were evaluated using the Wechsler Intelligence Scale for Children, Fourth-Edition. Participants were grouped into one of four treatment groups: non-HRT, early hormonal therapy (EHT), hormonal booster treatment (HBT), or both EHT and HBT (EB). These treatment groups were further segregated by timing of 47,XXY diagnosis (prenatally (PRE) vs. postnatally (POST)). HRT was administered before five years of age, based on the participant's pediatric endocrinologist's assessment.

Results: ANOVA testing in PRE-boys revealed a significant difference in WM for the treatment groups ($F(3,84)=7.467$, $p=.000174$). Post-hoc comparisons indicated a significant difference in WM scores ($p=.0092$) between the non-HRT ($M=92.37$, $SD=17.83$) and EHT groups ($M=106.39$, $SD=12.01$). Significant WM differences existed between the non-HRT ($M=92.37$, $SD=17.83$) and EB ($M=111.08$, $SD=10.02$) groups ($p=.0021$).

Conclusion: WM is an important executive functioning skill that affects learning, higher-order thinking, achievement, and the ability to self-monitor. This study, to our knowledge, is the first to suggest a potential positive effect of HRT improving WM outcomes in this common but rarely diagnosed population. WM deficits are often seen in these boys as early as 3 years old; however, since 47,XXY does not present with distinctive facial features, this syndrome is typically not recognized as a possible underlying etiology for an undiagnosed boy struggling with everyday WM-related tasks. Further investigation to understand the relationship between the biology of testosterone/androgen deficiency, timing of diagnosis, and WM in boys with 47,XXY is warranted.

Keywords: 47,XXY, Klinefelter syndrome, Working Memory, Hormonal Replacement Therapy, Executive Functioning

POSTER 23: Food-Related Problems in Klinefelter Syndrome? A Probable Case of Pica

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Background: Obesity is frequent in adult Klinefelter (KS) subjects, mainly associated with hypogonadism and the metabolic syndrome. Rarer are the descriptions of altered food and eating disorders (FED) in KS in developmental age. We report about a 17 yrs old boy affected by KS and Pica defined in the DSM5 by the persistent eating of nonnutrive, nonfood substances.

Methods: Clinical history, clinical and psychometric evaluation, imaging.

Results: A., a 17 year old boy, was born at term at the end of a preeclamptic pregnancy (weight: 2.940 kg). A. is the eldest of two children and parents are not consanguineous. He was breastfed and weaning started at the age of 4 month. At the age of 1 year, A. underwent screening for celiac disease and any food intolerance emerged. Normal psychomotor milestones, delayed sphincter control (3 years). Since the first months evacuation difficulties persisting during infancy as chronic constipation. This behaviour was associated with soiling and faecal incontinence. Chronic constipation still persists. At the age of 2 yrs, following karyotype because of dysmorphisms (hypertelorism and epicanthic fold, low set-ears), a diagnosis of KS(XXY) was formulated. Array CGH genetic testing did not document any adjunctive genomic variation. A rectal biopsy ruled out Hirschsprung disease. During early childhood, A. was used to assume non-food substances (candles, pencils, crayons). Currently, A. bites pieces of clothes and straps of garments. He presents an important onychophagy, currently limited to the fingers, while in the past extended to the toes. IQ is borderline (IQ 79, VIQ75, PIQ8 8); SCQ, EAT scores are in normal range; BIS score: 18 (attentional impulsivity). Brain MRI is normal.

Conclusion: Comorbidities between food-related problems and genetic syndromes are frequent mainly for Prader Willi syndrome. However, no significant association between KS and Pica, a rare FDA, has been reported in our knowledge.

Keywords: Klinefelter Syndrome, Pica, FED

POSTER 24: Autism Needs to be Considered in Children with Down Syndrome

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Background: To analyse levels and profiles of autism symptoms in children with Down syndrome (DS) with and without diagnosed autism spectrum disorder (ASD) and to specifically study the groups with severe Intellectual disability (ID).

Methods From a population-based cohort of 60 children with DS (age 5 – 17 years) with 41 participating children, scores obtained from the Autism Diagnostic Observation Schedule (ADOS) Module-1 algorithm were compared between those with and without diagnosed ASD. Children with DS and ASD were also compared to a cohort of children with idiopathic ASD.

Results: Children with DS and diagnosed ASD had significantly higher ADOS scores in all domains compared to those without diagnosed ASD. When the groups with DS, with and without ASD, were restricted to those with severe ID, the difference remained. When the children with DS and ASD were compared with a group with idiopathic autism, the ADOS profiles were broadly similar.

Conclusion: A considerable proportion of children with DS has ASD but there is also a group of children with DS and severe ID without autism. There is a need to increase awareness of the high prevalence of autism in children with DS to ensure that appropriate measures and care are provided.

Keywords: Autism spectrum disorder, Autism phenotype, Down syndrome, Intellectual disability

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POSTER 25: Poster xx :The Cognitive Profile of Turner Syndrome

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Background: The behavioural phenotype of Turner syndrome is characterized by average to lower-than-average total IQ, with relative strengths in verbal cognition and deficits in visou-spatial ability. Deficits in executive functions and social cognition are common. We aimed to provide detailed data on cognitive profiles and neuropsychiatric traits (Autism Spectrum Disorder and Attention Deficits/Hyperactivity Disorder) in a sample of Swedish women with Turner syndrome. The results might contribute to a better definition of the neuropsychiatric features specific to the syndrome.

Method: A sample of adult women with Turner syndrome (N=30) was assessed with the Wechsler Adult Intelligence Scale for collection of cognitive profiles. The Autism Quotient and the Adult Self-Report Scale 1.1. were collected for measures of neuropsychiatric traits.

Results: Participants showed cognitive profiles characterised by a slightly below average total IQ score in comparison to normal population (mean 94.6, range 72 – 126). The results showed elevated scores within verbal function and decreased scores within perceptual reasoning, in comparison to the individual total IQ. Analysis of subtests revealed that verbal comprehension scores were relatively high and all remaining subtests showed relatively low scores, except for Arithmetic and Matrix Reasoning, which showed average scores. The prevalence of self-rated ADHD was 23% in our sample, while autistic traits were equal to population means.

Conclusion: Our results resemble previous research on cognitive profiles in Turner syndrome, with relative strengths in the verbal domain and weaknesses in the procedural domain. However, they suggest a higher level of fluid intelligence than in previous studies. The high prevalence of ADHD in our sample indicates that these deficits might be under-diagnosed in women with Turner syndrome in Sweden.

Keywords: Turner syndrome, Behavioural phenotypes, Cognitive profiles, Rare disorders, Autism, ADHD

POSTER 26: Turner Syndrome: Mental Health and Social Skills from Childhood to Adolescence

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Background: The psychopathology of children and young people with Turner Syndrome (45,X; TS) has been well-documented, but no previous studies have assessed neurodevelopmental disorders (NDD) alongside emotional and conduct disorders. We aimed to comprehensively examine mental health, NDD and social skills in TS from childhood to emerging adulthood.

Methods: Participants aged 4 to 25 were recruited through the UK Turner Syndrome Support Society and NHS clinics. Standardised assessments were administered to caregivers. (1) The Strengths and Difficulties Questionnaire (SDQ; n=124) is a brief emotional and behavioural screening questionnaire. (2) The Development and Wellbeing Assessment (DAWBA; n=100) is rated by clinicians to generate DSM-V diagnoses. It assesses anxiety, depression, conduct, autism spectrum disorders (ASD), attention deficit hyperactivity disorders (ADHD) and tic disorders. It has been used in the English national surveys of child and adolescent mental health. (3) The Social Responsiveness Scale-2 (SRS-2; n=117) measures autistic symptomatology. All assessments are widely used and well-validated.

Results: DAWBA analysis showed elevated rates of mental health disorder compared to female norms. Notably, 33% met criteria for at least one mental health diagnosis. 23% met criteria for ASD, 11% for anxiety disorders and 12% for ADHD. Mean SDQ total scores were raised compared to female norms ($t_{(123)}$=12.89, p<0.0001). Emotional dysregulation was positively correlated with age (r=0.23, p=0.01), whereas hyperactivity problems (r=-0.47, p<0.0001) and conduct problems (r=-0.2, p=0.025) were negatively correlated with age. Mean total SRS-2 scores were in the 'moderately impaired' range (M=65.5, SD=14.9). Autistic symptomatology was rated as 'severe' in 27.4%. Participants have 46 times the risk (relative risk) of having severe autistic symptomatology compared to female norms.

Conclusion: Girls with TS have higher rates of mental health disorders and NDD than general population females. Difficulties with hyperactivity/inattention and conduct resolve developmentally, however emotional problems increase.

Keywords: Turner syndrome, social skills, sex chromosome aneuploidy, mental health, psychopathology

SSBP Syndrome Sheets 2019

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

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

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

Prevalence

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

Physical Phenotype

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

Life expectancy/natural history

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

Behavioural and cognitive characteristics

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

Outcome

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

Websites:

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

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Patricia Howlin, August 2017,

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CHARGE Syndrome

First Description

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

Genetics/aetiology

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

Incidence/prevalence

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

Physical phenotype

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

CHARGE has become the most common cause of congenital deaf-blindness (after "other" and "unknown"). These difficulties are present due to missing or malformed semi-circular canals and otoliths. Swallowing difficulties are common due to cranial nerve dysfunction. Other problems include gastroesophageal reflux, airway difficulties, chronic otitis media, sinusitis, detached retina, scoliosis, chronic constipation with megacolon, and sleep disturbances.

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

Behavioural and psychiatric characteristics

There is variability in the presence of behavioural difficulties. Behaviour has been described as very goal directed and persistent, socially interested but socially immature, demonstrating high rates of repetitive behaviour and sensation seeking, including problems with self-regulation and transitioning between activities. The behaviours have led to diagnoses of autism, attention deficit/hyperactivity disorder, obsessive-compulsive disorder, and tic disorder. It has been proposed that pain, sensory issues, and anxiety, which produce problems with self-regulation, are major sources of the behavior (Hartshorne, Stratton, Brown, Madavan-Brown, & Schmittel, 2017).

Neuropsychological characteristics

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

Useful websites/associations for more information

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

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Timothy S. Hartshorne, May, 2019

Coffin-Lowry Syndrome

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

Genetics and molecular biology

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

Incidence / Prevalence

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

Physical features and natural history

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

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

Female heterozygotes show variable involvement that can range from short stubby digits with normal appearance to quite marked facial dysmorphism.

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Ventriculomegaly has been observed in several affected males and females.

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

Behavioural characteristics

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

Cognitive function of female carriers may be variably affected: it can range from normal intelligence to moderate mental retardation. Frequently, they are reported to have learning difficulties at school. Obesity , depression, psychotic behavior including schizophrenia) have been described in a few female carriers. Epilepsy may occasionally develop. Stimulus-induced Drop Episodes (SIDE) may occur in response to unexpected auditory of tactile stimulus (Rojnueangnit et al, 2013).

Available guidelines for behavioural assessment/ treatment/management

There is no specific treatment. Sensorineural hearing deficit should be addressed very early to improve the development and quality of life of the patients. Treatment for individuals with CLS who experience drop attacks includes medications such as valporate and clonazepam or selective serotonin uptake inhibitors. If stimulus-induced drop episodes occur with great frequency, use of a wheelchair may be required to prevent falling and injury (Hunter, 2005).

Useful Websites

U.S. National Library of Medicine (NLM), Genetics Home Reference
https://ghr.nlm.nih.gov

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André Hanauer, June 2010
Revised Stewart Einfeld, 2015.
Revised Navid Dadlani & Stewart Einfeld, June 2019

Coffin Siris

First description and alternative names

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

Genetics and molecular biology

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

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

Incidence/prevalence

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

Physical features and natural history

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

Behavioral and psychiatric characteristics

A few individuals have been described as aggressive or self-injurious while some have been characterized as having happy personalities..

Neuropsychological characteristics

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

Available guidelines for behavioral assessment/ treatment/management

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

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

Useful Websites

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

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Revised Stewart Einfeld, 2015
Revised Navin Dadlani & Stewart Einfeld, June 2019

Cornelia de Lange syndrome

First description and alternative names

Cornelia de Lange Syndrome is named after a Dutch paediatrician who first described the syndrome in 1933. The disorder is occasionally referred to as Brachmann de Lange Syndrome after a German doctor who is also thought to have described a patient with the syndrome in 1916.

Incidence/prevalence

CdLS has an estimated prevalence of 1 in 10,000 to 30,000 live births (Kline et al., 2018), although this is thought to be an underestimate, with more mildly affected individuals increasingly being identified.

Genetics

CdLS is caused by a deletion on the *NIPBL* gene on chromosome 5 (locus 5p13) in up to 80% of cases (Gillis *et al.*, 2004; Krantz *et al.*, 2004; Miyake *et al.*, 2005; Tonkin *et al.*, 2004, Huisman *et al.*, 2013). Mosaicism for *NIPBL* mutations is identified in 23% of individuals [Huisman et al., 2013]. Additional mutations in *SMC3* on chromosome 10 (Deardorff et al., 2007), X linked *SMC1a* and *HDAC8* genes (Deardorff et al., 2012a; Musio et al., 2006) and more recently identified *RAD21*, *ANKRD11* and *BRD4* mutations (Deardorff et al., 2012b; Kline et al., 2018) are reported to account for a smaller proportion of cases. All genes are involved in the structure and regulation of the cohesin complex which is crucial for neural maintenance and repair (Deardorff et al., 2012b; Liu & Krantz 2009). It is probable that there are further unidentified mutations relevant to the cause of CdLS.

The *NIPBL* gene is expressed in the developing skeleton and soft tissue of the limbs, hands, spinal column, face and head including the ear canal, the atrial and ventricular areas of the heart, oesophagus, trachea and lungs (Tonkin et al. 2004). Individuals with *NIPBL* mutations show large variability in presentation but a larger proportion of these individuals appear to be more severely affected by the syndrome with more severe intellectual disability and limb abnormalities (Gillis et al. 2004; Bhuiyan et al. 2006; Huisman et al., 2017). In contrast, mutations in *SMC1a* and *SMC3* have currently been found to result in a milder presentation of the CdLS phenotype with less severe intellectual disability and fewer physical abnormalities (Deardorff et al. 2007; Huisman et al., 2017).

Physical features and natural history

Individuals with CdLS typically have a low birth weight, small stature, upper limb abnormalities (25%) and hirsutism, although those with a milder presentation seem less affected by these problems (Deardorff et al. 2007; Kline et al. 2007). Distinctive facial features, including: synophrys, long, thick eyelashes, a long and prominent philtrum, a thin upper lip; and a downturned mouth appear characteristic of most individuals with the syndrome (Kline et al. 2007). CdLS is associated with many health problems (for overview see Kline et al., 2018). Some of the most commonly occurring problems include: gastro-intestinal disorders, hearing and eye abnormalities, cardiac and genito- urinary problems. Gastro-intestinal disorders are particularly problematic in CdLS.

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

Behavioural characteristics

Self-injurious behaviour is generally thought to be more common in people with CdLS than in the general intellectual disability population (Sloneem et al. 2009) and reported to be influenced by anxiety, sleep problems and social reinforcement for some individuals (Arron et al., 2006; Huisman et al., 2018; Kline et al., 2018). There is a notable association between self-injurious behaviour and associated medical conditions, particularly gastrointestinal reflux (Huisman et al., 2018; Luzzani et al., 2003).

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

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

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

Neuropsychological characteristics

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

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

Age related change

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

Available guidelines for behavioural assessment/ treatment/management

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Useful websites/associations for more information

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- CdLS World: www.cdlsworld.org
- FIND resources: www.findresources.co.uk
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J Moss & C Oliver, July 2010.
Updated: J. Moss, L. Nelson & C. Oliver, July 2015
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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

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

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

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

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

Neuropsychological characteristics

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

Useful websites/associations/resources for more information

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

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P Tunnicliffe, J Moss, & C Oliver, July 2015.

Down Syndrome

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

Epidemiology

Incidence varies globally, in part due to choices surrounding prenatal testing. In the USA, 1 in approximately 800 live born children will have DS (de Graaf, Buckley, & Skotko, 2015). Ireland has the highest incidence in Europe (1 in 546 live births) (Ni She & Filan, 2014), In England and Wales, approximately 1 in 1000 live born children have DS (Wu & Morris, 2013) however in Iceland, no infants with DS have been born during a five year period (Wise, 2016).

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

Life expectancy has increased dramatically over the past 50 years, now reaching approximately 60 years of age (Englund, Jonsson, Zander, Gustafsson, & Annerén, 2013). While rare, it is not unheard of for some individuals to live past the age of 70. This means the numbers of individuals with DS are increasing, despite prenatal testing.

Genetics

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

This excess of genetic material leads to a dysregulated expression of certain genes (Letourneau et al., 2014). The functional impact of these changes could be a direct result of the action of the proteins expressed in excess by the Hsa21 genes, or indirectly, through the proteins that they regulate. In any case the effect will be different according to the protein involved (Fillat et al., 2014). The nuclear compartments of trisomic cells may also undergo modifications of the chromatin environment influencing the overall transcriptome (Letourneau et al., 2014).

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

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

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

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

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

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

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

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

Physical and Mental Health

There is considerable variation in the penetrance of the phenotype associated with trisomy 21, however certain characteristics are more common. For example, intellectual disability is present to some degree in all patients with full trisomy 21, as is muscle hypotonia and AD neuropathology after the age of 35 years (Antonarakis, Lyle, Dermitzakis, Reymond, & Deutsch, 2004). Motor dysfunction is highly prevalent among individuals with DS, who can exhibit clumsy sequences of movements, and poor control in programming motor sequences, their timing and force. Motor dysfunction in DS is accompanied by hyporeflexia and reduced muscular strength and tone (Dierssen, 2012). Most adults with DS are of short stature (70%), with a characteristic facial appearance. The eyes seem to slope upwards and outwards as a result of alterations in the structure of the surrounding tissues. The nose has a wide bridge, and the head an unusual shape ("brachycephaly"). Protruding tongue is present in 45% of children with DS. Limb abnormalities include a single transverse crease on the palm (85%), a large cleft between the first and second toes, and relatively short upper arms.

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

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

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

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

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

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

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

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

Behavioural characteristics

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

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

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

No significant associations between age and the range or severity of any behavioural and emotional items were found in adult DS subjects without dementia. This suggested a more positive pattern for ageing adults with DS until symptoms of dementia develop (Makary et al., 2014).

Cognitive characteristics

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

Most children and adults with DS function in the mild or moderate range, and cognitive abilities tend to be higher among people with mosaicism (Papavassiliou et al., 2015).

Early language milestones, such as babbling, are typically met within a similar period to typically developing infants. However, by school age a specific impairment in expressive language is evident in relation to most individuals' receptive language abilities (Grieco et al., 2015). Difficulties in syntax expression and comprehension are common throughout the lifespan, and verbal working memory is a noted weakness.

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

Deficits in attention and executive functioning are seen at all ages. Individuals with DS show particular difficulties with inhibition but in terms of planning, for example, may take longer than mental-age matched controls, but can achieve similar levels of performance (Grieco et al., 2015).

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

Alzheimer's disease and dementia

In adults with DS, neuropathological changes typical of Alzheimer's disease usually develop by the fourth decade of life, and dementia is now considered to be the leading underlying cause of death in older adults with DS (Hithersay et al., 2018). On post-mortem examination, almost all adults with DS over the age of 35 have the brain changes characteristic of Alzheimer's disease (i.e. amyloid plaques and neurofibrillary tangles) (Mann & Esiri, 1989; Wisniewski, Wisniewski, & Wen, 1985).

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

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

Clinical signs and symptoms of AD in DS include early changes in memory and attention (Firth et al., 2018; Startin et al., 2019). Executive functioning, behavioural and personality changes may also be seen (Ball et al., 2006; Dekker et al., 2015; Lautarescu, Holland, & Zaman, 2017).

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

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

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

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Annapia Verri, September 2014

Updated by Rosalyn Hithersay, Sarah Pape and Andre Strydom 2019

Foetal alcohol syndrome/ Alcohol related neurodevelopmental disorder

First description and alternative names

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

Genetics and molecular biology

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

Incidence/ prevalence

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

Physical features and psychiatric characteristics

Characteristic facial features include short palpebral fissures, thin (flat) upper lip, flattened philtrum, flat midface. Growth retardation less than the 10th percentile for height and weight. Low birth weight for gestational age, decelerating weight over time

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

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

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

Neuropsychological Deficits

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

Brain structural abnormalities

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

Brain neurotransmitter and neurophysiological abnormalities

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

Available guidelines for behavioral assessment/ treatment/management strategies

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

Useful websites /associations for more information

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

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

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Fragile X Syndrome and Fragile X-associated Disorders

First described

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

Genetic aspects

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

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

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

Incidence/Prevalence

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

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

Physical Features in Fragile X Syndrome

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

Life expectancy/Natural history

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

Behavioural characteristics

Intellectual impairment is variable and correlates with the molecular findings. Those with higher levels of FMRP, such as females and those with an unmethylated full mutation or mosaic status (some cells with the premutation and some with the full mutation), will have a higher IQ because they are producing more FMRP. Verbal intelligence usually exceeds performance abilities in both affected males

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and non-learning disabled female carriers, although about 10% of patients will be non-verbal or will have very low verbal abilities. Particular difficulties with numeracy, visuospatial skills and visual motor abilities are common. The rate of intellectual development diminishes with age, particularly after puberty. This will lead to a lower IQ overtime, although there is no regression of abilities but instead a lack of abstract reasoning development which holds the IQ lower with age.

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

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

Treatment

Individuals with fragile X syndrome typically respond well to a stimulant medication after 5 years of age. Clonidine or guanfacine have been helpful for hyperarousal and hyperactivity in children under 5yo or older. Selective serotonin reuptake inhibitors (SSRIs) help anxiety and can be used even in those under 5, although activation can be seen in about 20%, requiring a lowering of the dose or discontinuation. Atypical antipsychotics, most notably aripiprazole, when used in low dose helps to stabilize mood, decrease aggression, improve attention, and decrease anxiety. Minocycline is a targeted treatment for fragile X because it lowers matrix metalloproteinase 9 (MMP9) levels and a controlled trial demonstrated efficacy in young children with fragile X syndrome. Arbaclofen, a GABAB agonist has also been shown to benefit patients with fragile X syndrome particularly those with ASD or social deficits although a controlled trial in adolescents and adults did not show efficacy. However, limited efficacy is seen in younger children ages 5 to 11 treated with arbaclofen. The metabotropic glutamate receptor 5 (mGluR5) antagonists have not demonstrated efficacy in adolescents or adults with fragile X syndrome in controlled trials but a new trial in children ages 3 to 6 with AFQ056 combined with a parent implemented language intervention (PILI) through Skype is ongoing currently. A controlled trial of a low dose of sertraline (2.5 to 5.0 mg) in children ages 2 to 6yo demonstrated efficacy in developmental profiles and is often used clinically. Anecdotal cases have demonstrated a benefit from metformin treatment in language skills and behavior. Metformin has rescued the fragile X phenotype in animal models and it is now undergoing a controlled trial in children ages 6 to 25yo at multiple centers. A multicenter trial of a topical ointment with cannabidiol (CBD) is also undergoing a controlled trial at multiple centers to target anxiety. In addition, a new GABA agonist Gaboxidol is also undergoing studies of two dosage regimens. These studies will likely lead to many more

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

Resources

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

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Randi Hagerman MD, August 2015
Updated Randi Hagerman MD, May 2019

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47,XXY (Klinefelter Syndrome)

First description and alternative names

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

Genetics and molecular biology

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

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

Incidence/prevalence

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

Physical features and natural history

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

Behavioral and psychiatric characteristics

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

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

Neuropsychological characteristics

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

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

Available guidelines for behavioral assessments/ treatment/management

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

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

Useful websites/associations for more information

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

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Updated: The Focus Foundation, USA, 2017

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Lesch-Nyhan Disease (LND)

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

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

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

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

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

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

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,

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

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

Treatment:

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

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

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

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

Life expectancy:

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

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

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15. CMS standard: 482.13. (e) (6).) Exception: "Repetitive self-mutilating behavior. If a patient is diagnosed with a chronic medical or psychiatric condition, such as Lesch-Nyhan Syndrome, and the patient engages in repetitive self-mutilating behavior, a standing or PRN order for restraint to be applied in accordance with specific parameters established in the treatment plan would be permitted. Since the use of restraints to prevent self-injury is needed for these types of rare, severe, medical and psychiatric conditions, the specific requirements (1-hour face-to-face evaluation, time-limited orders, and evaluation every 24 hours before renewal of the order) for the management of violent or self- destructive behavior do not apply."
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(Prepared by Gary E. Eddey, August 2014

Mowat-Wilson syndrome

First description and alternative names

Mowat *et al.* (1998) first delineated the syndrome and suggested it was caused by a microdeletion in chomosome 2q22 – 2q23 or by a de novo mutation of a gene within this region. In 2001, Cachuex *et al.* (2001) and Wakamatsu *et al.* (2001) independently identified the cause of the syndrome to be deletions or intragenic mutations of the ZEB2 gene. Zweier *et al.* (2002) later proposed the name "Mowat-Wilson syndrome", abbreviated to MWS.

Incidence/prevalence

MWS has an estimated prevalence of 1 in 50,000 – 70,000 live births (Mowat & Wilson, 2010), though several authors suggest it may be more common than originally thought (Adam *et al.*, 2006; Engenheiro *et al.*, 2008; Garavelli & Cerruti-Mainardi, 2007; Mowat, Wilson, & Goossens, 2003). While early publications reported more males than females due to the ascertainment bias of hypospadias and Hirschsprung disease (HSCR), more recent reports suggest MWS affects both genders equally (Garavelli & Cerruti-Mainardi, 2007; Zweier *et al.*, 2005).

Genetics

Mowat-Wilson syndrome is caused by mutation or deletion of the ZEB2 gene, previously known as the Zinc Finger Homeobox 1 B gene (ZFHX1B) located on chromosome 2 at the location 2q22 (Cacheux *et al.*, 2001; Mowat *et al.*, 2003; Wakamatsu *et al.*, 2001). Over 110 different mutations have been reported (Dastot-Le Moal *et al.*, 2007), the majority of which result in premature stop codons. However, in recent years, cases with a milder phenotype resulting from missense mutations and partial loss of ZEB2 function have been reported (Ghoumid *et al.*, 2013; Yoneda *et al.*, 2002; Zweier, Horn, Kraus, & Rauch, 2006).

While most cases of MWS occur de novo, germline mosiacism is possible and the recurrence rate is estimated at around 2.3% (Cecconi *et al.*, 2008).

Physical features and natural history

Mowat-Wilson syndrome is characterised by a distinct constellation of facial features in association with variable congenital anomalies. Medical complications can include seizures (in around 80% of cases), Hirschsprung disease (40 – 50%), severe constipation in those without Hirschsprung disease, agenesis of the corpus callosum (around 45% of cases), congenital heart defects (around 50%), kidney and urogenital anomalies (around 50%). Microcephaly occurs in over 80% of cases (Garavelli & Cerruti-Mainardi, 2007; Mowat & Wilson, 2010). Structural eye anomalies and strabismus have been noted in some people with MWS (Mowat & Wilson 2010), and one case of MWS with bilateral sensorineural hearing loss has been reported (Abdalla & Zayed, 2013).

The facial characteristics of Mowat-Wilson syndrome change with age (Garavelli *et al.*, 2009). Babies generally have a square face with a prominent, triangular-shaped chin, and a broad, saddle nose. With age, the face lengthens, and adults with MWS have a very long chin, with prognanthism. By adulthood, the nose has lengthened, has a convex profile and overhangs the philtrum.

Other facial features include:

- Hypertelorism (wide set eyes)
- Deep set but large eyes
- Open mouth
- M shaped upper lip
- High arched palate
- Full or everted lower lip
- Fine, sparse hair
- Large uplifted ear lobes with a central depression – arguably the most recognisable feature of MWS. The uplifted lobes remain with age but the depression becomes less marked.
- Flat feet and long, tapering fingers and toes are common, as is short stature.

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Behavioural characteristics

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

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

Neuropsychological characteristics

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

Useful websites/associations for more information

- Website 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.

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,

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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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June 2015

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Prader-Willi Syndrome (PWS)

First description

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

Genetics and molecular biology

PWS results from the absence of expression of the paternal allele of paternally expressed/maternally imprinted genes at the chromosomal locus 15q11-q13 (the PWS critical region). The commonest genetic mechanisms leading to PWS are: a) a de novo deletion at the PWS critical region on the chromosome of paternal origin (~ 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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Updated by Sarita Soni, May 2015

Rubinstein-Taybi syndrome (RTS)

Prevalence

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

Genetics

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

Physical features

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

Behavioural characteristics

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

It has also been suggested that individuals with RTS may be at increased risk of mood instability, as they get older, such as anxiety and depression. However, more evidence is needed to corroborate this finding.

Cognitive characteristics

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

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Laurie Powis, Jane Waite and Chris Oliver, August, 2014
Georgina Edwards, Laurie Powis, Jane Waite and Chris Oliver (updated March 2019)

Rett Syndrome (RTT)

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

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[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 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

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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.

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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Gillian Townend & Friederike Ehrhart : 2016

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Triple-X syndrome (47,XXX)

First description and alternative names

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

After the first description there was a period of research in biased populations, e.g. in institutes for mentally retarded, asylums and forensic psychiatric hospitals (Olanders 1975). In 1974 it was decided to screen 200,000 newborns for chromosomal disorders in several hospitals. The triple-X cases in this study have been evaluated several times for at least 20 years. These newborn-screening studies yielded unbiased data (Robinson et al. 1990).

Genetics and molecular biology

In triple-X syndrome there is an extra X chromosome in all cells or, in mosaic cases, in almost all cells. Most of the cases are diagnosed through prenatal diagnostic examinations.

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

Whether incomplete silencing of the extra X chromosome, the prolonged cell cycle during division or epigenetic phenomena are relevant during development in 47,XXX requires further research.

Incidence/prevalence

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

Physical features and natural history

Tartaglia et al. (Tartaglia et al. 2010) reviewed the physical findings in triple-X syndrome. Since most of these findings (such as clinodactyly, epicanthal folds or hypertelorism) are minor, the majority of cases remain undiagnosed. Tall stature is common, and especially the underarms and legs are longer. The girls have their growth spurt earlier than do controls. Clinically speaking, decreased head circumference is probably the most important common feature; there seems to be a relationship between head circumference and level of cognitive functioning (Ratcliffe et al. 1994). Motor and coordination abilities seem to be somewhat retarded, and the girls are sometimes described as being clumsy. Neuroimaging studies revealed a smaller head circumference and a lower brain volume (Patwardhan et al. 2002).

Since 1959 many physical disorders associated with a triple-X finding have been reported, most of which do not exceeding the population prevalence numbers. But there are some disorders that seem to be more common in triple-X cases: urogenital anomalies, (partial) epilepsy and Premature Ovarian Failure (POF) and infertility (Tartaglia et al. 2010, Stochholm et al. 2010).

Behavioral and psychiatric characteristics

Low self-esteem seems to be the most common feature (Otter et al. 2010). Social anxiety/shyness and executive dysfunction are common in triple-X girls (van Rijn et al. 2013, van Rijn and Swaab 2015, Lenroot et al. 2014). Social cognitive problems are common in triple X girls, probably due to language disorders (Bishop et al. 2011). Another study in triple X girls showed a developmental pattern that resembled the development of girls with autism with mild or late presenting autism symptoms (van Rijn et al. 2014). Challenging behaviour may be the result of any of these developmental difficulties. Triple X girls living in a stable family function better than triple-X girls in a unstable family (Netley 1986). The triple-X girls seem to

be less able to cope in a stressful environment. After leaving school, most of the girls will find a job that reflects their non-verbal abilities (Robinson et al. 1990).

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

Scientific progress through neuroimaging findings

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

Neuropsychological characteristics

Data on intelligence are consistent, indicating that the full scale IQ's are almost 20 points lower than what would be expected in the family (Robinson et al. 1990). Whether the girls show problems in reading or arithmetic is not uniformly reported in the case reports. Clinical experience suggests that some difficulties during arithmetic lessons result from language disorders. Mild or serious academic problems/special educational needs are quite common (Robinson et al. 1990, Bishop et al. 2011). Further research is needed to confirm the findings on increased prevalence of attention problems and to explain these attention problems: are they due to receptive language disorder, auditory processing disorders or attention deficit disorder (ADD)(Lenroot et al. 2014)? Clinical experience in treating ADD with medication suggests that the treatment is less effective than in 46,XX cases; however, controlled treatment studies are lacking (Leggett et al. 2010).

Available guidelines for behavioral assessment/ treatment/management

There is no evidence-based management guideline, although Otter et al. have proposed a guideline of medical and behavioural assessment (Otter et al. 2010).

Useful websites/associations for more information

- The Dutch parents' support website: http://triple-x-syndroom.nl/. This website shows many links to scientific papers and useful links, e.g. links to international chat pages for parents and triple-X girls/women. Scientific papers and syndrome sheets are available in several languages: English, French, Spanish, German and Dutch.
- Unique, a parents support group from the United Kingdom provides a syndrome sheet with information on physical and behavioural developmental issues: http://www.rarechromo.org/information/Chromosome_X/Triple_X_syndrome%20Trisomy_X%20FTNW.pdf.
- The KS&A (Klinefelter Syndrome and Associates) website provides a brochure and more: http://www.genetic.org/Knowledge/Brochures.aspx . Especially parents and triple-X girls/women in the United States will find opportunities to meet experts, other parents and triple-X girls/women. KS&A is active in fundraising for the support of scientific research.

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Tuberous Sclerosis Complex (TSC)

First description and alternative names

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

Genetics and Molecular Biology

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

Incidence/prevalence

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

Physical features and natural history

Wide variability of expression. The previously used "diagnostic triad" (of epilepsy, intellectual disability and characteristic facial skin lesions) is seen in only about 30% of people with the disorder. TSC is multi-system and can include hamartomatous growths affecting the brain, skin, kidneys, heart, eyes, teeth, lungs and other organs. About 70-80% of people with TSC have a lifetime history of epilepsy. Diagnosis is based on meeting clinical criteria for the disorder (Northrup, Krueger et al., 2013). Mutations are identified in >90% of individuals with clinically confirmed TSC.

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

Behavioural and psychiatric characteristics

Tuberous Sclerosis is associated with a wide range of behavioural, psychiatric, intellectual, academic, neuropsychological and psychosocial difficulties. The term TAND (TSC-Associated Neuropsychiatric Disorders) was coined in 2012 as a summary term for all the bio-psycho-social aspects of the disorder (Krueger et al., 2013; de Vries et al., 2015) and a TAND Checklist has been developed to aid clinical teams to screen for TAND (de Vries et al., 2015; Leclezio et al., 2015). At the behavioural level, TSC is associated with high rates of mood/anxiety, overactive/impulsive, sleep/eating, dysregulated behaviours (aggression and tantrums), and many autism-related behaviours. At the psychiatric level, neurodevelopmental disorders

are common, with autism spectrum disorders (ASD) in 40-50%, ADHD and attention-related disorders in 30-50% and intellectual disability in ~50% of individuals. TSC is one of the medical conditions most commonly associated with ASD. In adolescents and adults, very high rates of anxiety and mood disorders are reported. Psychotic disorders should raise the possibility of seizure-related psychopathology (de Vries et al., 2015).

Neuropsychological characteristics

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

Available guidelines for behavioural assessment/ treatment/management

- International consensus guidelines were drawn up for the assessment of cognitive and behavioural problems in TSC (de Vries *et al.*, 2005). These were revised and are augmented by the new guidelines on screening and assessment (Krueger, Northrup *et al.*, 2013) and by the TAND Checklist (de Vries *et al.*, 2015; Leclezio *et al.*, 2015).
- There are currently no TSC-specific treatments available for the neuropsychiatric manifestations of TSC. Clinicians should therefore use evidence-based interventions as for the general population.
- Targeted treatments using mTOR inhibitors are currently in clinical trials for TSC-associated neuropsychiatric disorders (TAND) (Curatolo, Moavero & de Vries, 2015; de Vries, Wilde, *et al.*, 2018), but these are not at present recommended outside clinical trials.
- The diagnostic criteria and management guidelines for TSC were revised in 2012 and were published in 2013 (Northrup, Krueger *et al.*, 2013; Krueger, Northrup *et al.*, 2013).

Useful websites/associations for more information

- www.tuberous-sclerosis.org
  [UK user/carer organization]
- www.tsalliance.org
  [USA user/carer organization]
- www.tscinternational.org
  [International user/carer organization]

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

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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.

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

Useful websites/Associations for more information

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

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David H Skuse, 2014

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

First descriptions and alternative names

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

Genetics/aetiology

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

Incidence/prevalence

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

Physical characteristics

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

Behavioural characteristics

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

Cognitive characteristics

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

Available guidelines for behavioural assessment/ treatment/management

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

Useful websites/associations for more information

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

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Linda Campbell : June 2016

Williams Syndrome (also known as Williams-Beuren Syndrome)

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

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

Incidence:
The condition is estimated to occur in 1 per 20,000 individuals although higher rates (1 in 7500) have been reported (Morris, 2017).

Physical phenotype and natural history:
The condition typically presents in infancy with difficulties in feeding, irritability, constipation and failure to thrive. The physical phenotype is remarkably consistent across the world (Kruszka *et al.*, 2018) and the principal characteristics are well summarised by Morris (2017). The main features include: endocrine and growth abnormalities (pre-natal growth deficiency, failure to thrive in infancy, infantile hypercalcaemia, hypercalciuria, hypothyroidism, early puberty); cardiovascular disease (mainly supravalvular aortic stenosis) and renal abnormalities; connective tissue abnormalities (hoarse voice, inguinal/umbilical hernia, bowel/bladder diverticulae, rectal prolapse, joint and skin laxity), and distinctive facies (broad brow, short nose, long philtrum, bitemporal narrowness, periorbital fullness, full lips, wide mouth, malocclusion, small jaw and prominent earlobes).

With age, subcutaneous tissue is lost, giving rise to a prematurely aged appearance. Premature greying of the hair occurs in many adults. A characteristic posture may develop with sloping shoulders, exaggerated lumbar lordosis and flexion at the hips and knees. Progressive multi-system medical problems have been reported in some adults, which can lead to premature death. These include cardiovascular complications, gastrointestinal problems and urinary tract abnormalities. Progressive joint limitations are also common.

Behavioural and psychological characteristics:
Most individuals have moderate to mild intellectual impairments, although some may be of low-average to average IQ (Royston *et al.*, 2019). Overall cognitive ability generally remains fairly stable across the life span (Fisher *et al.*, 2016) but verbal IQ is typically higher than non-verbal IQ and there are complex, and often subtle, pattern of peaks and valleys within each of these domains. Research into the nonverbal abilities of individuals with WS has highlighted particular deficits in domains such as number skills, planning, problem solving and spatial cognition. In contrast, face processing and some aspects of social cognition tend to be relative strengths. Within the verbal domain, auditory rote memory and receptive vocabulary are viewed as strengths, while spatial language (e.g. using spatial terminology), expressive vocabulary, syntax, semantics and grammatical comprehension are generally delayed (see Martens *et al.*, 2008; Skwerer & Tager-Flusberg, 2011; Royston *et al.*, 2019 for reviews); pragmatic language difficulties may also become more apparent with age (Van Den Heuvel *et al.*, 2016). Adaptive behaviour skills are often relatively poor (Howlin *et al.*, 2010) but research findings on the

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

Individuals with WS tend to show particular patterns of emotional and behavioural difficulties (Einfeld *et al.*, 2001;Morris, 2017). An intense drive for social interaction is one of the most characteristic traits and is evident from early childhood (Riby *et al.*, 2017). However, older children and adults with WS have difficulties making and sustaining friendships and because of their desire to make social contact they have a high risk of being bullied, exploited or abused (Fisher *et al.*, 2017; Fisher & Morin, 2017). Other difficulties include hyperacusis, attentional problems, impulsivity, and externalizing (oppositionality and aggression) and internalizing problems (anxiety and withdrawal) (Klein Tasman *et al.*, 2017; Royston *et al.*, 2019). A significant minority of children shows autistic-type symptoms (social communication deficits, stereotyped and repetitive behaviours; Klein Tasman *et al.*, 2018); however, reported rates of self-injurious behaviours are lower than in other genetic developmental disorders (Huisman *et al.*, 2018)

Rates of mental health problems in adulthood are high are high and include phobias, preoccupations and obsessions, depression, bipolar disorder and hypomania. The most commonly reported mental health problem is anxiety, which occurs more often in WS than in individuals with other developmental genetic disorders and is significantly more frequent than in the general population (Royston *et al* 2017; Stinton *et al.*, 2010; 2012)

Further information

- www.williams-syndrome.org.uk

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Patricia Howlin, 2014
Patricia Howlin, Updated 2019

Wolf-Hirschhorn syndrome

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

Genetics and Molecular Biology

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

Prevalence and Mortality

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

Physical Features

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

Behavioral and Neuropsychological characteristics

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

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Gene Fisch 2014

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47,XYY Syndrome

First description and molecular biology

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

Genetics and molecular biology

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

Incidence/prevalence

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

Physical features and natural history

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

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

Behavioral and psychiatric characteristics

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

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

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

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

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

Neuropsychological and neurological characteristics

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

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

Neuroimaging

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

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

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

Available guidelines of behavioral assessment/ treatment/management

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

Useful websites/associations for more information

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

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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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Acknowledgements

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

- **Jane Waite** and **Kate Woodcock,** the Local Organisers of the conference.
- **Liz Walmsley**, the SSBP Administrator
- **Rebecca Windram**, the SSBP Conference Administrator
- **Deborah White**, our graphic designer from Department of Shapes & Colours
- **Our Sponsors – The Castang Foundation, The Genetics Society, Guarantors of Brain, Tracksys, CamNtech, JIDR**
- **Members of the Scientific Committee**, for review of abstracts and posters
- **All keynote speakers**, for their time and expertise
- **SSBP Trustees** and **Executive Committee**
- **Members of the Kate Woodcock Research group** who contributed to conference organisation
- **Aston University**, for support in the subsidised use of venues, and for providing a travel grant to Dr Deborah Fidler to attend the conference.

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The 23rd SSBP International Research Symposium

Educational Day 10th September 2020 • Research Symposium 11th – 12th September 2020 • Oslo, Norway

Developmental disorders and behavioural phenotypes across the lifespan

The Society for the Study of Behavioural Phenotypes will be holding their 23rd Research Symposium in Oslo, Norway, on the 11th and 12th September 2020, the Education Day will be on 10th September. The theme will be: Developmental disorders and behavioral phenotypes across the lifespan.

We welcome you to Oslo, one of the greenest and most compact European capitals. Oslo is an important centre of maritime knowledge and home to some of the world's largest shipping companies, shipbrokers, and insurance brokers. In the city centre, the docks have transformed into luxurious seafront architectural marvels, and other pearls of Oslo's industrial past have been re-discovered and revamped into cafes, foodhalls, colleges, bars, and art galleries. From the city you can easily access the beautiful Nordic scenery.

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